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EDITORIAL

Metabolic brain function

Función metabolica del cerebro

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We all know that our brain requires oxygen and glucose to carry out the biochemical processes necessary for it to function, as it needs more energy than any other organ in the body. The average cerebral blood flow is 50 mL/100 g/min to ensure an average oxygen consumption at rest of 3.5 mL/100 g/min[1]. Glucose is the principal source of energy for the brain; however, it does not cross the blood–brain barrier freely. To enter the brain, it requires an active transport mechanism through the Glucose transporter 1[1,2].

The role of glucose in the brain has been known for a century. Variations in glucose levels cause changes in alertness; patients with hypoglycemia experience drowsiness, leading to stupor or coma if this decrease in glucose is persistent. The changes observed confirm the importance of glucose as fuel for the brain[2]. In this edition, Jiménez-Maldonado et al. report early signs of metabolic dysfunction in the brains of young adults with type 1 diabetes mellitus (DM1).

Glucose levels in the brain correspond to 10-25% of plasma levels, so there are variations after eating foods with hyperglycemia spikes and during fasting with hypoglycemia[3]. Variability in glucose levels can lead to long-term complications, such as cognitive complications[4]. In patients with DM1 and elderly patients with DM2, alterations associated with information processing speed, verbal fluency, attention, and memory have been identified[5].

In their study, Jiménez-Maldonado et al. evaluated verbal fluency using blood oxygen level-dependent signaling in functional magnetic resonance imaging in subjects with DM1 compared to healthy controls. Although they found no differences in cognitive assessment, they did find that patients with DM1 required the activation of larger brain areas, including subcortical regions such as the basal ganglia, to perform the tasks.

DM1 is most frequently diagnosed during childhood and adolescence, when changes in the central nervous system are taking place, meaning that variations in glucose levels can have repercussions. Acute hypoglycemia causes global cognitive impairments such as short-term memory loss. If hypoglycemia is severe, it can cause irreversible neurological damage due to diffuse necrosis of the cortex, or even death. Acute hyperglycemia can also cause impairments such as bradypsychia and inattention[6].

Therefore, it is important that patients receive adequate treatment and avoid extreme and non-physiological variability in glucose levels. The measurement of glycosylated hemoglobin (HbA1c) values has been used as an indicator of the degree of glucose control[7].

Diabetes continues to be a global health problem. In Mexico, the prevalence of diabetes in 2022 was 18.3%, occurring at older ages and among people with lower levels of education. Of all cases of diabetes, type 2 diabetes accounts for 90-95% of cases, and type 1 diabetes accounts for 5-10%[8]. Due to the high prevalence of DM2 in the population, cognitive impairments should be sought in this group of patients, and not only in patients with DM 1.

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As medical professionals, we recognize the association between diabetes and the presence of cardiovascular and cerebrovascular disease, kidney disease, and amputations. However, we must integrate the presence of cognitive impairment into the study protocol for patients with diabetes, using screening tests such as the Mini-Mental or the MoCA test, as well as more specific tests through neuropsychological assessment.

In conclusion, diabetes can interfere with the brain's metabolic function, which can lead to cognitive impairment. Therefore, we must prevent its onset by adequately controlling glucose levels through optimized treatment.

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ORIGINAL ARTICLE

A study of fMRI BOLD signals in verbal fluency tasks in young patients with type 1 diabetes mellitus

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Abstract

Objective: *Our study aimed to evaluate verbal fluency (VF) using the blood oxygen level-dependent (BOLD) signal on functional magnetic resonance imaging (fMRI) in subjects with type 1 diabetes mellitus (T1DM) versus healthy controls. This was done during the execution of several tasks with high cognitive demand.* **Methods:** *A total of 15 right-handed subjects with type 1 diabetes (nine males, six females, with 20.80 average age) and 15 healthy right-handed volunteers (20.93 average age) matched by sex, age, and years of education performed a VF task while undergoing fMRI.* **Results***: Both groups obtained similar cognitive performance, with no significant differences in intelligence (p = 0.424), cognitive flexibility (p = 0.258), semantic VF (p = 0.620), and only phonological VF was close to significance (p = 0.063), which implies that both groups behaved similarly. Although the VF task activated the expected brain areas, such as the prefrontal cortex, in both groups, a difference was detected in young people with T1DM, who required the activation of larger brain areas, including some subcortical regions, such as the basal ganglia, to perform the tasks.* **Conclusions***: Our findings indicate that even among young adults with T1DM, there may be early signs of changes in metabolic brain function. This highlights the crucial role of the health sector in neuroscience to identify and address potential early cognitive changes in T1DM patients.*

Keywords: *Type-1 diabetes mellitus. Verbal fluency. Blood oxygen level-dependent signal.*

Un estudio de las señales fMRI BOLD en la tarea de fluidez verbal en pacientes jóvenes con DM1

Resumen

Objetivo: *Nuestro estudio tuvo como objetivo evaluar la fluidez verbal utilizando la señal dependiente del nivel de oxígeno en sangre (BOLD) en imágenes por resonancia magnética funcional (MRf) en sujetos con DM1 frente a controles sanos. Esto se llevó a cabo durante la ejecución de varias tareas con alta demanda cognitiva. Nuestra hipótesis era que ambos grupos responderían adecuadamente a nivel cognitivo, pero que habría diferencias en la actividad metabólica, según lo evaluado por los métodos de MRf.* **Métodos:** *quince sujetos diestros con diabetes tipo 1 (nueve hombres y seis mujeres, con una edad media de 20,80 años) y quince voluntarios diestros sanos (con una edad media de 20,93 años), emparejados*

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por sexo, edad y años de educación, realizaron una tarea de fluidez verbal mientras se sometían a una resonancia magnética funcional. **Resultados:** *Ambos grupos obtuvieron un rendimiento cognitivo similar, sin diferencias significativas en inteligencia (p = 0,424), flexibilidad cognitiva (p = 0,258) y fluidez verbal semántica (p = 0,620), y solo la fluidez verbal fonológica se acercó a la significación (p = 0,063), lo que implica que ambos grupos se comportaron de manera similar. Aunque la tarea de fluidez verbal activó las áreas cerebrales esperadas, como la corteza prefrontal, en ambos grupos, se detectó una diferencia en los jóvenes con DM1, que necesitaron la activación de áreas cerebrales más amplias, incluidas algunas regiones subcorticales, como los ganglios basales, para realizar las tareas.* **Conclusiones:** *Nuestros hallazgos indican que, incluso entre los adultos jóvenes con DM1, pueden aparecer signos tempranos de cambios en la función metabólica del cerebro. Esto pone de relieve el papel crucial del sector sanitario en el campo de la neurociencia para identificar y abordar los posibles cambios cognitivos tempranos en los pacientes con DM1.*

Palabras clave: *Diabetes tipo 1. Fluencia verbal. Señal BOLD.*

Introduction

There is still no consensus on a definition of executive function (EF)[1,2]. However, it is widely accepted that EF includes a range of processes involved in complex behaviors such as decision-making, planning, abstract reasoning, self-monitoring, cognitive flexibility, behavioral inhibition, verbal fluency (VF), and working memory[1,3,4]. In summary, EFs help organize goal-directed actions[5], where the self plays a key role in modulating socially appropriate behaviors, all of which are complex skills.

Although there is still some debate about whether specific skills are related to EF, it is widely accepted that these skills are not uniform and involve moderately interconnected constructs[6]. In general, regardless of the type of ability, these skills are controlled by different regions of the frontal cortex, especially the prefrontal cortex[7]. However, several studies[8,9] have shown that some EF tasks, such as VF and switching tasks, also engage other areas such as the superior left parietal cortex[8,9]. In addition, the frontal cortex is closely connected to various parts of the central nervous system, such as the limbic system, indicating that emotional behavior can also be considered part of EF[1]. It is also important to note that VF depends on neurodevelopment[10] and may be linked to a perspective of functional interconnectivity[11].

The VF task, which is one of the tasks used to assess executive functioning, involves generating words that belong to a specific category or start with a certain phoneme within a limited time (usually 60 s)[1,12]. VF also requires inhibiting words that do not belong to the requested group and involves the ability to determine, update information, and follow specific procedures, making VF a key component of neuropsychological assessment[1,12].

VF tasks consist of two parts: (1) clustering and (2) switching[13]. In the first part, the subject uses a category until it is finished; the second part requires switching from one category (or cluster) to another. Both parts require inhibiting words that do not belong to the chosen category[12-14].

Functional magnetic resonance imaging (fMRI) studies of VF tasks in healthy subjects have shown activation in the medial prefrontal cortex[8], left inferior temporal lobe[14,15], left inferior frontal gyrus (LIFG)[15,16], and posterior parietal cortex[8]. Although the variety in the activation regions reported by different authors may result from task heterogeneity, another explanation highlights the specific verbal task used; the semantic fluency task is linked to temporal brain regions because it involves semantic memory, whereas the supramodal EF within the semantic or phonologic task depends on the frontal lobe[16].

VF, as a subdomain of executive functioning, is usually affected in other diseases such as schizophrenia[17], temporal lobe epilepsy[18], or frontal lesions[13], with less evidence in metabolic disorders.

In addition, some diseases exhibit patterns of changes in cognition and executive functioning at various levels. Severe or repeated hypoglycemia has been shown to cause cognitive impairment and neuronal death, likely because neither neurons nor glial cells can store glucose; therefore, over time, brain structure or function deteriorates, with the hippocampus being particularly vulnerable to these changes[19]. Diabetes mellitus, especially type 1, is a chronic disease that begins in childhood and adolescence, disrupting the balance of glucose and insulin, which affects different organs and systems, including the brain. Some cognitive deficits have been observed in individuals with type 1 diabetes mellitus (T1DM), notably in working memory, attention, EFs, visuospatial skills, and processing speed[19-22]. These alterations vary depending on

comorbidities, hospitalizations, hypo- or hyperglycemia episodes, or disease severity[19,23]; even social support can influence cognitive performance[24].

According to the World Health Organization, more than 463 million people have diabetes; in America, the number of diabetic patients is estimated at 62 million[25]. In addition, it is projected that 578 million people will have diabetes by 2030 and 700 million by 2040[25]. Approximately 3-5% of people with diabetes have type 1, which is one of the most common chronic diseases in childhood and adolescence[20,26]. In Mexico, the Ministry of Health reported that there are 542,000 children with T1DM, and nearly 78,000 develop it each year[27].

Although the severity of cognitive difficulties may be relatively mild, failures in cognitive functioning can be linked to a learning disorder[28,29] and may become more noticeable with poor glycemic control[30]. In addition, even a slight level of cognitive processing difficulty could interfere with or impair daily activities in adolescents and adults, especially when they need to solve complex cognitive problems, which could ultimately impact their quality of life[26]. Furthermore, fluctuations in long-term blood glucose levels have been associated with the development of stress, alexithymia, depression, and anxiety, among other clinical symptoms, and these changes also indicate a deficiency in the cognitive processing and regulation of emotional states[30,31].

Given that the intensity, chronicity, and impact of cognitive abilities in patients with T1DM vary due to multiple comorbidities and differences in glycemic control, and considering that T1DM begins early in life during a critical period for brain development, the adaptive form of metabolic balance requires more resources; therefore, identifying potential differences in activation patterns in brain regions during cognitively demanding tasks such as VF (semantic fluency) is crucial.

Therefore, there is an interest in understanding the differences between the neural substrates involved in solving high-demand cognitive tasks in cognitively normal individuals with T1DM and healthy controls.

Materials and methods

Participants

The study involved 15 right-handed individuals with T1DM (nine males and six females) and 15 healthy right-handed volunteers matched for age, sex, and years of education. All participants had normal or corrected-to-normal vision, average intelligence, and no history of neurological illness, psychiatric disorders, depression, addiction, or related conditions. Diabetic patients, diagnosed according to the American Diabetes Association criteria[32], had fewer than two hospitalizations in the past 2 years, maintained regular glycemic control, and had an average disease duration of 10 years. They did not have nephropathy, retinopathy, or any other clinical diabetes-related complications to be eligible for the study. This study received approval from the Ethics Committee of the "Hospital Civil Fray Antonio Alcalde" and the Neuroscience Institute at Guadalajara University, and informed consent was obtained from both patients and controls.

Stimuli and procedure

Our study used a unique pair of tasks (A/B): A, which assessed semantic VF by asking participants to produce words from a specific category, and B, a control task requiring subjects to recite the months of the year. This sequence was designed to activate brain regions involved in semantic VF.

We used a block design, with eight blocks per condition (A and B) and eight rest blocks between tasks; before each task, participants read a sign with an instruction reminder (Fig. 1). Each block included a beep or brief sound at 60 Hz for 225 ms, followed by 1500 ms allowed for responses, totaling 12 stimuli per block. The auditory stimulation was delivered through headphones to reduce scanner noise, and the session lasted 6 min and 12 s (Fig. 2). We used a modified paradigm of Gurd et al.[8]

All participants completed similar training 1 week before the scanner session to ensure familiarity and comfort with the tasks. Before the fMRI scan, plasma glucose levels were measured using an Accu-Check active glucometer. The task stimuli were presented using E-prime studio v.2.0 (Psychology Software Tools, Inc., 2013), and the images were projected through a Google system.

Image Acquisition: A 1.5 Tesla MR scanner (general electric healthcare system, Milwaukee, Ill) with a functional imaging T2∗-weighted gradient was used to obtain 32 contiguous 4 mm thick axial slices with the following parameters: repetition time (TR) = 3 s, echo time (TE) = 60 ms, field of view = 256 mm, matrix size = 64 × 64, and voxel dimensions = 4 × 4 × 4 mm, covering the whole brain. The experiment was conducted in a single session with two runs, each lasting 6 min and 12 s. The instructions and sounds for each response were presented using E-Prime software with a license.

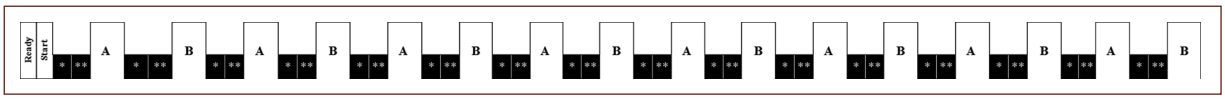

Figure 1. Experimental design.

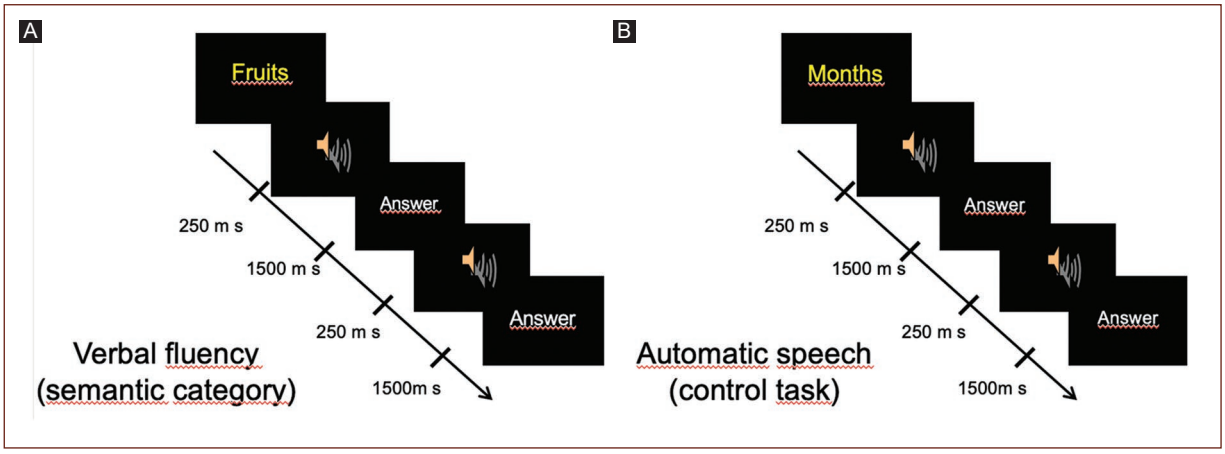

Figure 2. A and **B:** specific task.

Data analysis

Each experimental task involved 124 brain volumes; due to the experimental design, 12 brain volumes per task were discarded, leaving 112 for subsequent analysis. The images were preprocessed and statistically analyzed with the SPM8 software package (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). The images were spatially realigned, readjusted to the voxel size, and normalized according to the Montreal Neurological Institute and Talairach coordinates. For smoothing, a Gaussian kernel filter was applied three times the voxel size on the x-, y-, and z-axes.

The behavioral data were analyzed using the Statistical Package for the Social Sciences version 20, and statistical significance was set at 0.05.

Table 1. Participants baseline

	T1DM (n = 15)	Controls (n = 15)
Years with the disease	10 ± 3.47	-
Latest glycated hemoglobin	9.2 ± 2,87	-
Age	20.80 ± 4.47	20.93 ± 4.52
Education	12.20 ± 2.78	12.80 ± 3.00
Intelligence quotient	103.80 ± 9.88	109.20 ± 28.19
Verbal fluency (verbs)	18.93 ± 5.74	22.86 ± 4.91
Verbal fluency (semantic)	23.21 ± 5.96	24.14 ± 3.46
Verbal fluency (phonological)	11.86 ± 4.16	14.21 ± 3.40
Glucose level before fMRI (mL/dL)	217.67 ± 92.74	97.00 ± 10.06

T1DM: type 1 diabetes mellitus; fMRI: functional magnetic resonance imaging.

Results

Behavioral and cognitive results

The total sample included 15 individuals with T1DM and 15 healthy controls, with characteristics shown in table 1. Both groups exhibited similar cognitive performance, with no significant differences; they all had normal IQ, semantic, phonological, and VF, as well as cognitive flexibility and planning skills, indicating comparable cognitive abilities.

Since the behavioral data showed similar ratings between groups as expected, there was no difference between the groups in terms of age ($t[28] = -0.81$, $p = 0.936$; $d = 0.015$) or education level ($t[28] = -0.567$, $p = 0.575$; $d=0.10$), but a significant difference in glucose level was observed ($t[28] = 5.01$, $p = 0.000$; $d = 0.68$). We studied T1DM without cognitive alterations. Therefore, the behavioral results aligned with our expectations.

Table 2. Percentage, mean, and standard deviation of correct/incorrect responses for type 1 diabetes and controls

Type of tasks	T1D		Controls	
	Percentage	Mean (SD)	Percentage	Mean (SD)
Task A. Fluency Correct response Incorrect response	 87.08 0.83	 41.80 ± 4.91 0.40 ± 0.699	 93.75 0.45	 45.00 ± 5.24 0.22 ± 667
Task B. Automatic speech Correct response Incorrect response	 100	 48.00 ± 0.00	 99.08 0.91	 47.56 ± 1.33 0.44 ± 1.33

SD: standard deviation.

The average number of correct and incorrect responses per task was entered into a mixed-measures analysis of variance (ANOVA) with task (semantic fluency and automatic language) as a within-subject factor and group (type 1 diabetes vs. controls) as a between-subject factor, as shown in table 2.

As expected, there was no difference between the two groups (intragroup factor) in correct or incorrect responses. However, task complexity (VF vs. automatic speech) mainly influenced correct responses, and both groups responded similarly to the two tasks (Table 3).

Table 3. Mixed measurements ANOVA

Behavioral response	gl	F	Sig.	η^2	1-β
Correct answers (tasks)	1	17.748	0.001	0.511	0.978
Correct answers (groups)	1	3.075	0.098	0.153	0.380
Incorrect answers (tasks)	1	0.106	0.748	0.006	0.061
Incorrect answers (groups)	1	1.301	0.270	0.071	0.190

ANOVA: analysis of variance.

Imaging results

All the neuroimaging analysis results were statistically significant at the 0.01 level. The first step was analyzed separately for activations in each of the tasks: A (verbal semantic fluency) and B (automatic fluency). Based on the averages of activation in each group by experimental condition (Table 4), the main activation cluster in T1DM patients during the VF task was located in the cerebellum, followed by the medial and superior frontal gyri in the left and right hemispheres, respectively, as well as the hippocampal areas in both hemispheres. These findings highlight the importance of this research. In comparison, healthy controls showed greater activation in the frontal-precentral gyrus and cerebellum than T1DM patients, in whom cortical activations were more prominent (Fig. 3).

The second step involved analyzing the interactions using full factorial ANOVA, which showed the main effects of two between-group factors – task (semantic vs. automatic fluency) and group (type 1 diabetes vs. controls) – as well as their interaction. The inferential statistics are presented in table 5.

In the group factor analysis, three significant activation clusters were identified: two in the left hemisphere, one in the medial precentral frontal gyrus (BA 6), and the other in the culmen of the cerebellum (part of the superior vermis), with the third in the right medial temporal gyrus (Brodmann's area [BA] 22) (Fig. 4).

The interaction between tasks showed greater activation in T1DM patients than in controls, mainly in the prefrontal, precentral, and anterior cingulate areas (Fig. 5).

Discussion

The present T1DM sample and healthy controls did not show significant differences in their cognitive performance or behavioral task scores. This was expected due to the characteristics of our T1DM group, which had adequate glycemic control, no comorbidities, and good socio-economic functioning. This result aligns with other studies[33]. However, it has also been reported that T1DM patients performed slightly worse in inhibitory control[34] or working memory tasks despite maintaining reasonable diabetes control[35]. T1DM patients experience significant glycemic fluctuations throughout the day. In this study, although T1DM individuals did not show cognitive differences compared to a group of healthy controls before the fMRI scan, their blood glucose levels were above average. Since glucose level is an inherent factor (but not necessarily the cause) of metabolic changes, the variation in this variable between the groups does not appear to impact behavioral performance.

Table 4. Main activations, task A, semantic fluency

Groups	Z max	Cluster	Talaraich coordinates			H	BA	Area
			x	y	z			
T1DM	3.752	110	10	–72	–26	R	-	Cerebellum (pyramid)
	3.239	54	2	8	66	R	6	Superior frontal gyrus
	3.234	17	–26	–44	10	L	-	Hippocampus
	2.360	1	30	-44	10	R	-	Hippocampus
Controls	3.744	20	–26	–48	6	L	30	Parahippocampal gyrus
	2.746	8	18	–68	–26	R	4	Cerebellum (uvula)
	2.523	1	62	–4	18	R	6	Precentral frontal gyrus
	2.437	1	50	–8	34	R	-	Precentral frontal gyrus
	2.430	3	6	–76	–30	R	-	Cerebellum (pyramid)

T1DM: type 1 diabetes mellitus; Z max: maximum score; x, z, and y: spatial axes; H: hemisphere; BA: Brodmann area probabilistic citoarchitectonic mapping of activations with respect to BA.

Table 5. Effects of activations

Factors	F value	p	Cluster	Talaraich coordinates			H	BA	Area
				x	y	z			
Groups (T1DM vs. controls)	8.845	0.004	4	–62	0	22	L	6	Precentral frontal gyrus
	8.603	0.004	8	–26	–28	–22	L	-	Cerebellum-culmen
	7.822	0.007	5	70	–40	2	R	22	Medial temporal gyrus
Task (semantic vs. automatical fluency)	9.065	0.003	14	42	16	22	R	46	Medial frontal gyrus

T1DM: type 1 diabetes mellitus; F: F of Snedecor; p: P value; x, z, and y: spatial axes; H: hemisphere; BA: Brodmann area probabilistic cytoarchitectonic mapping of activations with respect to BA.

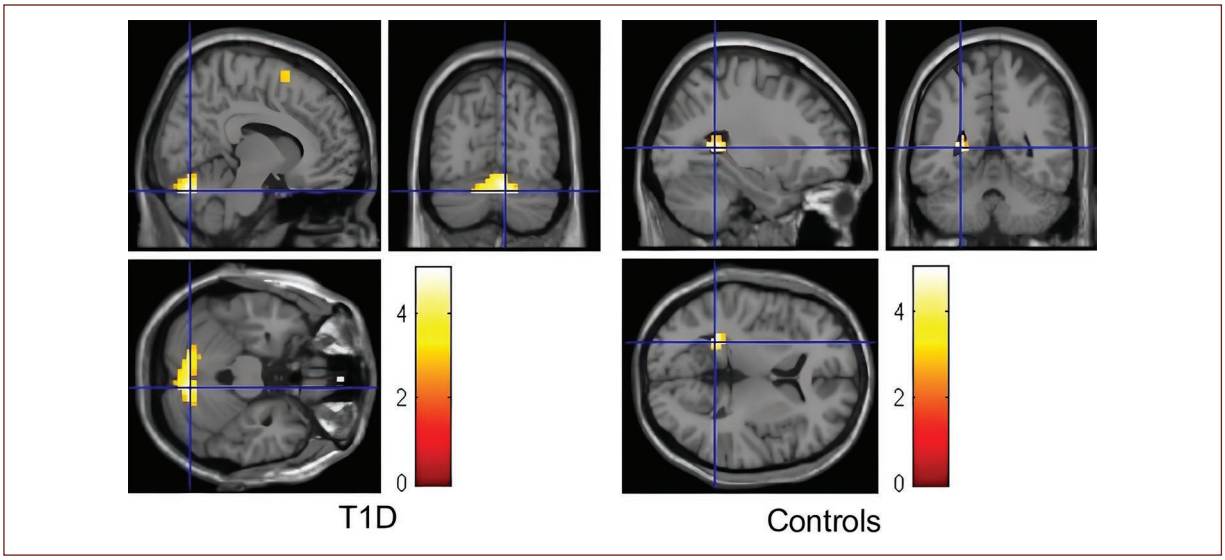

Figure 3. Image of sagittal, coronal, and temporal slices showing the average number of activations for each group of the verbal fluency task; the intersection indicates the main activation cluster.

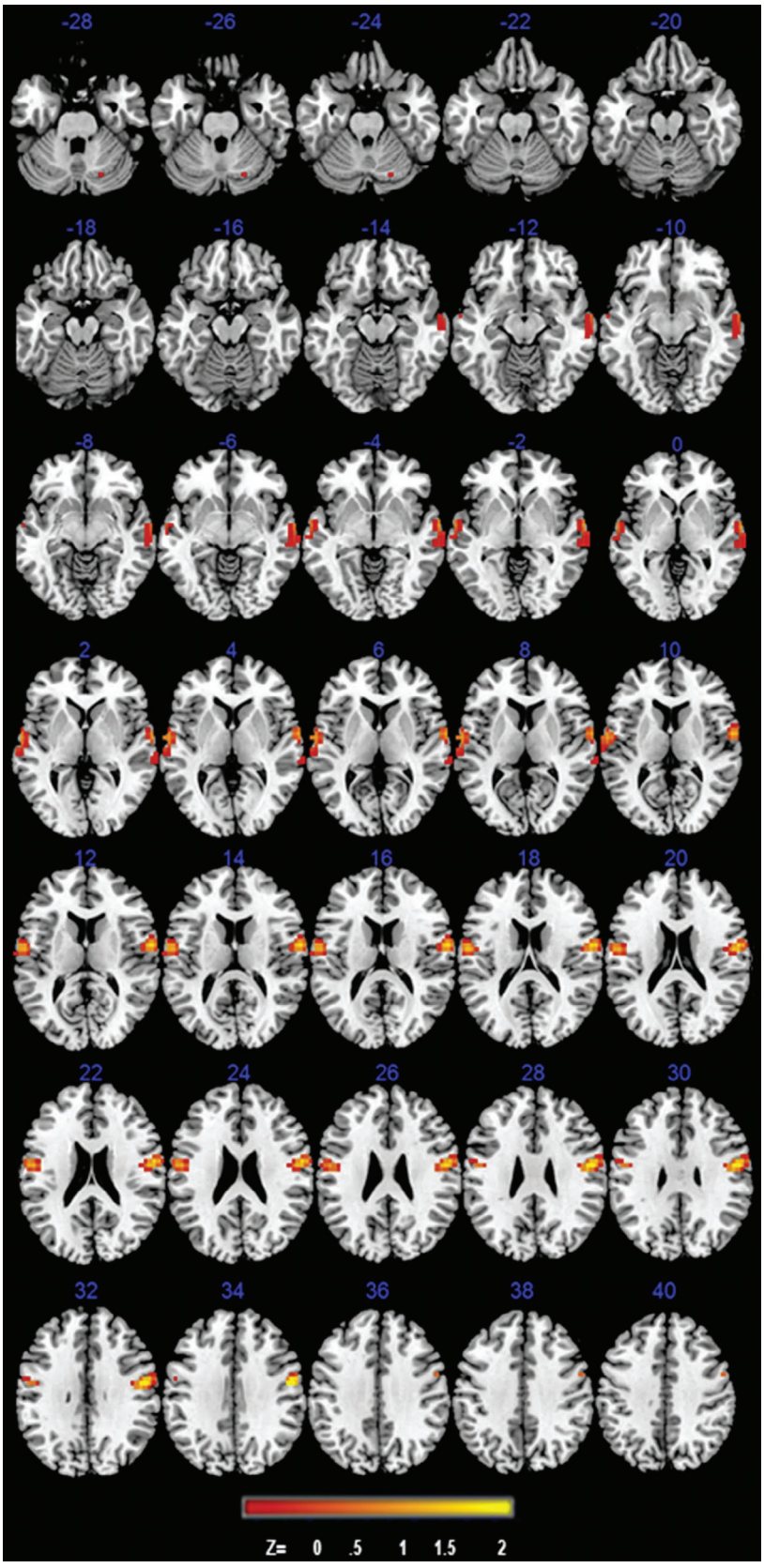

Figure 4. Brain activations, group factor, neurologic view (left-right).

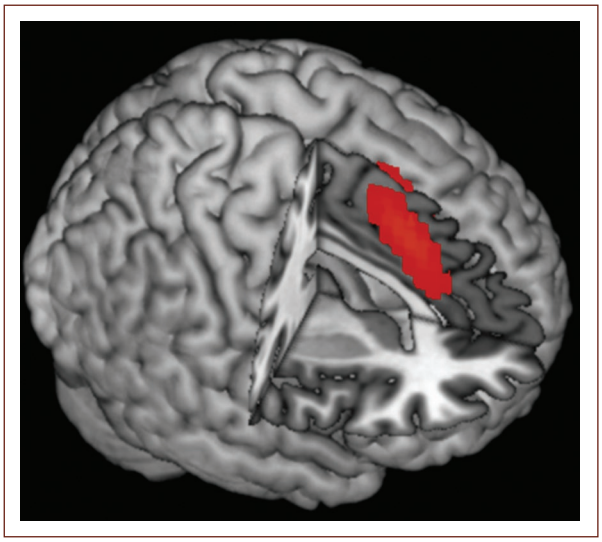

Figure 5. Reconstruction average image of the interaction between verbal fluency versus automatic speech tasks. Shades in red correspond to subjects with type 1 diabetes and shades in blue to control subjects.

The cognitive tasks of interest in VF have been described as activating several related brain areas, including prefrontal regions, especially the dorsolateral area, LIFG, anterior cingulate cortex, and cerebellum[8,14,15,36]. We observed these activations in both groups, particularly in the right hemisphere in the T1DM group; however, such activations were not evident in the overall group average.

Although the LIFG has been strongly associated with VF tasks, including both semantic and phonological ones[8,16,37], its absence from the group averages does not mean that this area is not involved. This could be explained by several factors: (a) the task was straightforward, such as a common category (fruits)[37], and (b) when averaging across all subjects, the activation was not visible, probably because the effect did not last long enough to generate a significant blood oxygen level-dependent signal.

In addition to activations in regions of the dorsolateral prefrontal cortex, both in terms of the average across all groups and within each group, we observed abundant activations in motor and premotor areas, mainly in the premotor cortex corresponding to BA[6]. This can be explained by the verbalization required to complete the task.

By analyzing frequencies in the VF tasks, activations were observed in both groups in the temporal regions, especially in the fusiform and temporopolar gyri (BA 38), which have been previously seen in both hemispheres[36]. In healthy control participants, the highest activations in the temporal lobe corresponded to Wernicke's area BA 22 (also bilaterally), which could be due to the strategy used or the task's low difficulty, as these factors can affect performance[38].

Our results emphasize that the cerebellum is predominantly activated, as reported in most tasks and interactions in other studies[38]. In this work, we observed activations in several regions of the cerebellum, and this structure has infrequently been linked to VF tasks[39].

Since both groups showed similar behavioral responses, it was difficult to differentiate T1DM patients from controls at the cognitive response level. However, differences can be identified in the brain structures involved in producing these responses; although T1DM patients need regulation of areas linked to the VF task, the intensity or clusters of activation are much higher than those of controls.

Conclusion

We must address several limitations in our study, one related to the fMRI scan performed on a 1.5 Tesla scanner, and the other concerning the sample size. However, the results can still be considered valid from both a clinical perspective and based on the findings, given that it is uncommon to evaluate individuals with this metabolic condition who do not have cognitive dysfunction but show different brain organization compared to those without any alterations.

We strongly advocate for a more comprehensive understanding of brain function in patients with type 1 diabetes during cognitively demanding tasks. This knowledge will enable us to provide early attention to the potential development of cognitive impairment, a crucial aspect that is often overlooked in current health-service follow-up. The focus is currently on controlling metabolic status, ensuring adherence to medical treatment, and early detection of common organ complications targeted by illness, such as renal issues, retinal problems, and peripheral nerve damage. However, the prevention of cognitive decline is equally important, as it can significantly impact the quality of life for T1DM patients.

Based on the above, although we are hypothesizing, it would be advisable to conduct longitudinal studies to confirm possible changes in brain organization.

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The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics

Committee of Neuroscience Institute of Guadalajara University (ET112014-183).

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Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

Temporal lobe epilepsy and changes in the M-current

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Abstract

Objective: *Acquired alterations of ion channel function occur after status epilepticus (SE). Kv7 channels mediate a sustained outward current (IM) that exerts pivotal control over neuronal excitability. Here, we investigate if pilocarpine-induced SE alters M-channel activity by quantifying the IM.* **Methods:** *Hippocampal slices were prepared from adult rats after pilocarpine-induced SE, when the animal was showing 3–5 spontaneous recurrent seizures (SRS) a day. A group of untreated, age-matched rats was used as the control group. Recordings were made using the whole-cell configuration of the patch clamp technique and current clamp mode to measure the membrane time constant.* **Results:** *The IM measured amplitude in CA1 neurons from pilocarpine-SE rats was significantly reduced compared to the control group (control, 208.72 ± 25.49 pA, n = 15; pilocarpine-SE, 49.28 ± 6.17 pA, n = 11; p < 0.05, Student's t). The time constant was 27.7 ± 17.7 msec in the control group and 48.9 ± 5.5 msec in the pilocarpine-SE group, and was significantly different (p < 0.05).* **Conclusions:** *In this study, we demonstrated that the M-current amplitude is significantly reduced in CA1 pyramidal neurons after pilocarpine-SE. Considering the acute damage that SE induces, the silent interval between injury and the onset of spontaneous seizures, and the chronic epileptic state in which the M-current was measured, we can speculate about the lack of homeostatic regulation of the intrinsic properties of neuronal excitability.*

Keywords: *Hippocampus. M-current. Pilocarpine. Status epilepticus. Epileptogenesis.*

Epilepsia del lóbulo temporal y cambios en la corriente M

Resumen

Objetivo: *Las alteraciones adquiridas en la función de canales iónicos ocurren después del estado epiléptico (SE). Los canales Kv7 determinan una corriente de salida sostenida llamada corriente M (IM), que ejerce un control fundamental sobre la excitabilidad neuronal. Investigamos si el SE inducido por pilocarpina altera la funcionalidad del canal M mediante la cuantificación de la IM.* **Métodos:** *Se prepararon rebanadas de hipocampo de ratas adultas que presentaron de 3 a 5 convulsiones espontáneas recurrentes (SRS) al día, después de haberles provocado el SE por la administración de pilocarpina. Los registros se realizaron con la técnica de fijación de voltaje en la modalidad de registro de toda la célula (whole cell).* **Resultados:** *En neuronas piramidales de la región CA1 del hipocampo de ratas que experimentaron SE, la amplitud de la IM disminuyó significativamente comparada con el grupo control (control, 208.72 ± 25.49 pA, n = 15; pilocarpina-SE, 49.28 ± 6.17 pA, n = 11; p < 0.05, Student's t). Se cuantificó la constante de tiempo (τ) de relajación. La τ se modificó significativamente (48.9 ± 5.5 mseg en el grupo pilocarpina-SE) con respecto al grupo control (27.7 ± 17.7 mseg).*

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Conclusiones: *En este estudio demostramos que la amplitud de la IM se reduce significativamente en las neuronas piramidales CA1 después del SE provocado por pilocarpina. Al considerar el daño agudo provocado por el SE, el intervalo de silencio entre la lesión, el inicio de las convulsiones espontáneas y el estado epiléptico crónico en el que se midió la IM, nos permite especular sobre la falta de regulación homeostática de algunas de las propiedades intrínsecas de la excitabilidad neuronal.*

Palabras clave: *Hipocampo. Corriente M. Pilocarpina. Estado epiléptico. Epileptogénesis.*

Introduction

Temporal lobe epilepsy (TLE) is the most common type of epilepsy in humans. Animal models of TLE are particularly useful for studying the basic neural mechanisms involved in epileptogenesis. After the induction of pilocarpine-status epilepticus (pilocarpine-SE) alterations in ion channel function occur during the acute period[1], during chronic periods following the establishment of spontaneous seizures[2] or acute and chronic periods[3]. Ion channels play essential roles in regulating neuronal excitability through the release of neurotransmitters, the generation of synaptic responses, and the propagation of action potentials (APs) along dendrites and axons. The involvement of ion channels in epilepsy is evidenced by the alteration in their function induced by channel blockers that cause seizures in experimental animals[2,4,5]. The M-current (I_M) is a slow-activating, low-threshold potassium (K^+) current that exerts inhibitory control over neuronal excitability. This inhibition can act by the action of neurotransmitters on G-protein-coupled receptors, leading to increased excitability and reduced adaptation to the frequency of neuronal firing[6,7]. The K^+ channels that generate I_M belong to the KCNQ2 and KCNQ3 family, and mutations in these channels are associated with a form of childhood epilepsy called benign familial neonatal seizures[7-9]. These channels display slowly activating and deactivating K^+ currents with distinct electrophysiological and pharmacological properties, and the activation of muscarinic acetylcholine receptors suppresses them. Because K^+ channels are critical for establishing and stabilizing resting neuronal membrane potential, a loss of K^+ channels could support neuronal hyperexcitability[2,6,7]. This study evaluated the changes in I_M after pilocarpine-SE when spontaneous and recurrent seizures occur.

Material and methods

This study is experimental, basic research. All procedures and protocols used were approved by the Research and Ethics Committees of the Faculty of Medicine of the Universidad Nacional Autónoma de México, in strict compliance with the Norma Oficial Mexicana NOM-062-ZOO-1999[10], which complies with international guidelines for animal handling. The minimum number of animals was considered to achieve statistical significance and avoid suffering. All animals (male Wistar rats weighing 99 ± 33 g [29 ± 5 days old]) were obtained from the general vivarium of the Faculty of Medicine of the UNAM.

Pilocarpine model

The model used to induce TLE was the one described by Turski et al. in 1983[11], which is briefly mentioned: Animals were injected with atropine (1 mg/kg) subcutaneously and 20 min later the dose of pilocarpine (350 ± 30 mg/kg) was applied intraperitoneally. After the appearance of SE, the animals were kept under observation for about 120 min, then they were administered diazepam (5 mg/kg), 3-4 doses, at 1-h intervals, to counteract the severity of the seizures due to SE[12]. The surviving animals were kept under close surveillance and their hydration and feeding were taken care of in the laboratory, especially during the acute recovery period, about 1 week after SE. The animals were then observed for 8 h/day, 5 days a week with a video recording system to detect the occurrence of software requirements specification (SRS) like state 5 described in the kindling, Racine, 1972[13]. Once recovered from SE, the brains of the animals were used for electrophysiological recording in slices at variable periods of time. Rats of the same age and weight, kept under the same conditions, without being treated with pilocarpine, were used as a control group.

Hippocampal slices

To obtain slices from the hippocampal region, animals were deeply anesthetized with urethane (1.25 mg/kg i.p). They were perfused intracardially with cold (4 °C) artificial cerebrospinal fluid (ACSF) with concentrations in mM of 206 sucrose, 2.8 KCl, 1 $CaCl_2$, 1 $MgCl_2$, 2 $MgSO_4$, 1.25 Na_2HPO_4, 26 $NaHCO_3$, 10 D-glucose, 0.4 ascorbic acid, saturated with 95% O_2 and 5% CO_2, pH of 7.4 and

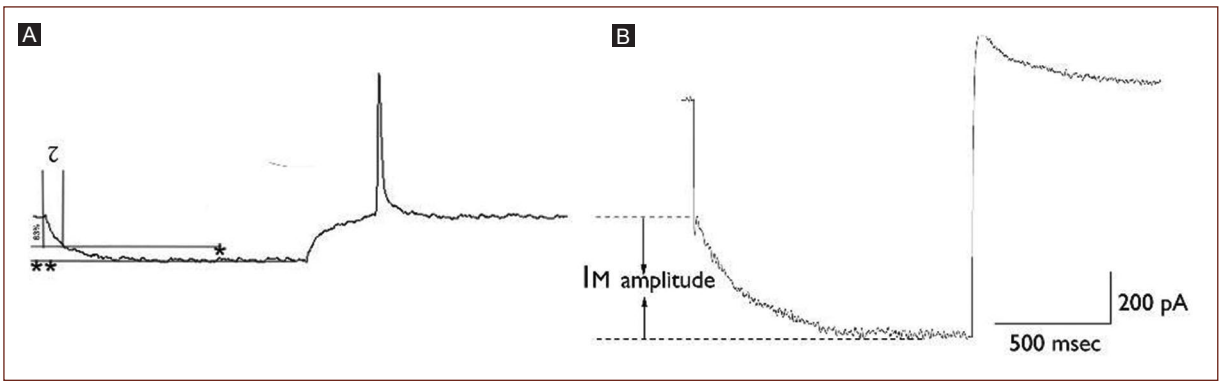

Figure 1. A: example of I_M quantification (voltage-clamp mode). The I_M relaxation amplitude is illustrated as the difference between the maximum peak and steady-state current values, **B:** changes in membrane potential (current-clamp mode) caused by applying negative current pulses of 15 nA and 50 m duration. *: indicates 63% of the maximum voltage change; **: indicates the maximum voltage deflection; τ: time constant.

osmolarity of 295 mOsm. Brains were rapidly removed and stored in cold (4 °C) ACSF containing in mM: 124 NaCl, 2.8 KCl, 2 $CaCl_2$, 2 $MgSO_4$, 1.25 Na_2HPO_4, 26 $NaHCO_3$, 10 D-glucose and 0.4 sodium ascorbate, with a pH of 7.4 and osmolarity of 295 mOsm, and saturated with 95% O_2 and 5% CO_2[14]. Hippocampal slices (350-400 μm) were obtained with a microtome-vibrator (Vibroslice 752; Campen Instruments Ltd. Lafayette, USA) and transferred to a beaker with oxygenated ACSF (95% O_2 and 5% CO_2) where they were kept at room temperature until recording. After 1 h of rest, each slice was transferred to a recording chamber in which 2 mL/min of oxygenated ACSF was continuously perfused at a constant temperature of 36 °C. The slice was held in place with a specifically designed cotton mesh. A microscope with Axioscop (Zeiss, Oberkochen, Germany) water immersion objectives (60×) equipped with a closed-circuit camera (Cohu Solid State Camera; San Diego, CA) was used. The cell bodies of the hippocampal pyramidal neurons were identified[14].

Electrophysiological recordings

Patch-clamp recordings were obtained in whole cell mode using an Axopatch 200A amplifier and pClamp 10 software (Axopatch 200A Molecular Devices, Sunnyvale, CA). Signals were filtered online at 1 kHz and digitized at 5 kHz during voltage-clamp recording. The signals were filtered at 10 kHz and digitalized at 50 kHz for the current clamp. The time constant (τ) was measured with current clamping before applying any drug to the recording chamber. The membrane time constant is the time for the potential to fall from the resting to a fraction of 63% of its final value in the charging curve when applying a small negative current pulse (0.15 nA for 30-50 m). (Fig. 1A) Digidata 1200, Axon Instruments). Filament-free borosilicate capillary glass (KIMAX-51) with an external diameter of 1.5 mm and an internal diameter of 1.0 mm (Kimble Products, USA) was used to make microelectrodes with a horizontal Flaming/Brown pipette puller model P-97 (Sutter Instrument, Novato, CA, USA). The recording electrodes were polished with a microforge and filled with a solution containing in mM: 175 KCl, 5 $MgCl_2$, 5 HEPES, 0.1 BAPTA, 5 Adenosine triphosphate, 0.3 guanosine triphosphate, and 0.1 leupeptin, with a pH of 7.4 adjusted with KOH and a resistance of 3.5-5.5 MΩ. The recordings were conducted under continuous perfusion of 1 μM tetrodotoxin (TTX) and the compound ZD7288 (4-Ethylphenylamino-1,2-dimethyl-6-methylaminopyrimidinichloride, H-channel blocker/HCN)[15], to dissect the I_M. The relaxation amplitude of the I_M was assessed in neurons from the brain tissue of control rats and pilocarpine-SE rats. For this, the difference between the maximum instantaneous peak current at the beginning of the command pulse of the voltage protocol and the steady-state current, just before the termination of the pulse, was used (Fig. 1B). The maintenance voltage to activate the I_M was set from –25 mV to –75 mV[16-18]. All chemicals were purchased from Sigma Chemical Co. (St. Louis, MO. USA).

Statistics

Commercial software (OriginPro 7.5, Microcal; Northampton, MA, USA) was used for graphing and

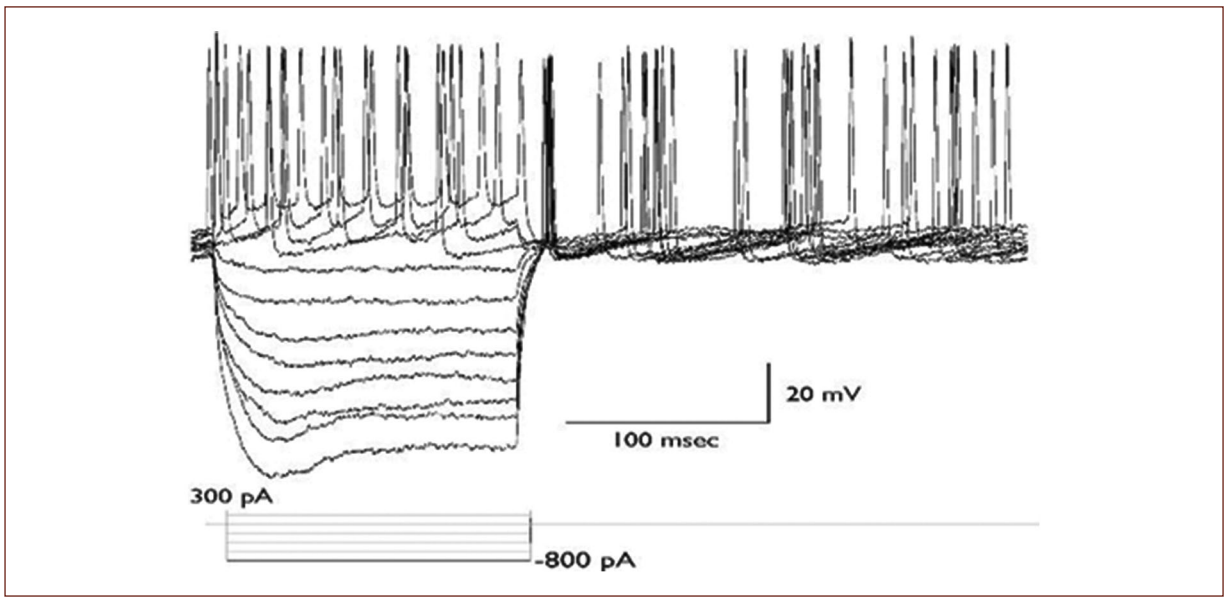

Figure 2. Example of membrane voltage response to current injection. Current pulses of 100-300 pA evoked a series of action potentials with little or no accommodation. During the injection of hyperpolarizing currents of −100 to −800 pA, neurons exhibited a voltage drop and showed a rebound upon cessation of hyperpolarization (see Methods).

statistical analysis. Student's T-test was used. Data are expressed as mean ± standard error of the mean, and a statistical significance value of $p < 0.05$ was considered.

Results

Spontaneous seizures after pilocarpine injection

In rats injected with pilocarpine, the average duration of SE was 46 ± 20 min. During the acute period of SE, there was a mortality rate of 66%. Eleven rats (34%) survived until electrophysiological recordings were obtained. During the 1st week after pilocarpine treatment, rats had, on average, one seizure per day. After 3 weeks of pospilocarpine, animals with SE exhibited 2-3 SRS daily. All animals were epileptic by the end of the 4th week.

I_M recording

I_M recordings were obtained from 60 pyramidal neurons in the CA1 region of the hippocampus. The current-clamp recording was performed at the beginning of each recording and before adding TTX to the recording chamber. Current-clamp pulses of + 300 to −800 pA were applied in 100 pA increments. Most cells showed an AP response with a gradual increase in the duration of the interval between potential and potential. This AP adaptation is characteristic of CA1 pyramidal neurons. Cells also showed the so-called "voltage sag" response, which consists of a slow hyperpolarization of the cell membrane due to the activation of the H current (Ih). Only cells that showed the characteristics of frequency adaptation and "voltage sag" were included in this study (Fig. 2). In voltage-clamp mode, responses were elicited by injecting voltage pulses of 800-1200 m duration from a holding potential of −25 mV to −75 mV in 10 mV increments (Fig. 3A). Fifty-five neurons in the control group showed on average resting membrane potential of −60 ± 0.75 mV, and sixty neurons in the pilocarpine-SE group had on average resting membrane potential of −55 ± 0.8 mV. This difference was not significant. Under these conditions, I_M appears as a slow, inward "relaxation" following an instantaneous (ohmic) drop in inward current. The current-voltage relationship revealed that increasing the amplitude of the voltage pulse increases the amplitude of I_M. The amplitude of I_M at −65 mV measured in CA1 neurons of pilocarpine-SE rats was significantly decreased compared with the control group (control: 208.72 ± 25.49 pA, n = 55; pilocarpine-SE: 49.28 ± 6.17 pA, n = 60; $p < 0.05$ Student's t-test) (Fig. 3B and

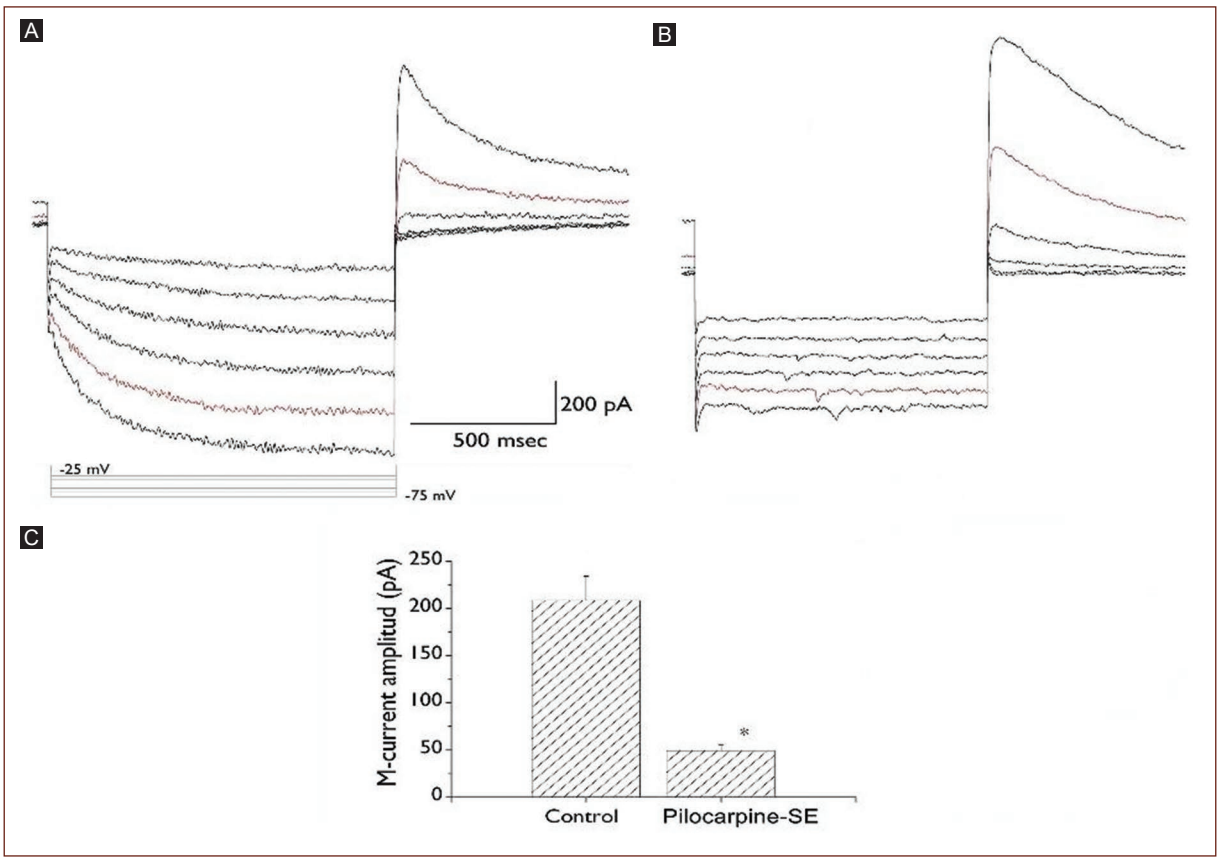

Figure 3. Representative recordings of current elicited in pyramidal neurons in hippocampal area CA1, obtained in voltage-clamp mode. **A:** control group, **B:** pilocarpine-SE group. Currents were elicited by applying hyperpolarizing voltage pulses of 1200 m duration from a holding potential of –25 mV to –75 mV in 10 mV increments (bottom of A). The I_M relaxation amplitude was determined by subtracting the instantaneous current at the beginning of the voltage pulse from the steady state at the end of the pulse, using the voltage change from –25 to –75 mV of the protocol (in red), **C:** summary of I_M amplitude. The amplitude of the I_M at –65 mV measured in hippocampal CA1 neurons of Pilocarpine-SE rats was significantly decreased compared with the control group (control, 208.72 ± 25.49 pA, n = 15; Pilocarpine-SE 49.28 ± 6.17 pA, n = 10; *p < 0.05, Student's T).

Table 1. The time constant of CA1 hippocampus neurons

CA1 neurones	Average time constant (τ)
Control (55 pyramidal neurons)	27.7 ± 17.7 msec
Pilocarpine-SE (60 pyramidal neurons)	48.9 ± 5.5 msec

The time constant of CA1 neurons was measured using whole-cell current-clamp recordings. An unpaired Student´s T-test revealed a significant increase in time constants in the pilocarpine-SE neurons compared to the control group ($p < 0.05$).

C). This study also assessed the cell surface by measuring the membrane capacitance. A significant increase in time constant was observed in pilocarpine-SE neurons (Table 1).

Discussion

In this study, we demonstrate that the amplitude of the I_M is significantly reduced in pyramidal cells of the CA1 area of the hippocampus after pilocarpine-induced SE. The channels responsible for this current are composed of KCNQ (Kv7) subunits[7], and mutations in most of them produce human and animal pathologies[19]. The importance of this current in neuronal excitability is established by the fact that a functional impairment of approximately 25% of KCNQ2/KCNQ3 heteromers seems to be sufficient to cause epileptogenesis[7].

The 23.6% reduction we observed in the I_M amplitude highlights the physiological importance of maintaining M-channel activity above a certain functional threshold. M-channels are activated by negative membrane

voltages. These non-inactivating Kv7 channels mediate a sustained outward current at negative potentials and may exert fundamental control over neuronal excitation and response patterns. M-channel activity potentially attenuates repetitive AP discharges[20]. This implies that a slight impairment of I_M converts the firing properties of neurons from a phasic pattern to a tonic pattern because M-channels may no longer function as efficient "brakes" in regulating neuronal excitability. Pharmacologically induced attenuation of M-channel activity dramatically increases neuronal firing and excitability *in vitro* such that a neuron with a phasic activity pattern can display a tonic activity pattern. Furthermore, the inhibition of synaptic M-channels can lead to increased propagation of evoked field potentials and facilitate the response to glutamate and/or GABA[21-24].

A transgenic mouse model, in which M-channel activity in the brain was reduced by mutation of KCNQ2 subunits and which suppresses M-channel activity, supported the observation that epileptic seizures, abnormal hyperactivity, attenuated afterhyperpolarization and some cognitive deficits presented by these transgenic animals may be associated with the alteration and consequent suppression of I_M[2,25]. Another known aspect to modify the state of the I_M channel is the administration of specific KCNQ blockers such as linopirdine or the compound known as XE991[2,26-28]. Administration of linopirdine causes epileptic activity in hippocampal slices and provides direct evidence of the involvement of KCNQ channels in the seizure process[26,29]. For this reason, it has been thought that these KCNQ channelopathies play an important role in human epilepsy, and it has been hypothesized that they occur after acquired disorders, such as the induction of SE. Therefore, the reduction in I_M amplitude observed could be part of the mechanism to explain the appearance of seizures after pilocarpine-induced SE, and changes in the time constant could reflect morphological alterations in the cell membrane that could be contributing to the generation of abnormal cell firing patterns. Considering the acute damage caused by SE, the silent interval between the lesion, the onset of spontaneous seizures, and the chronic status epilepticus in which I_M was measured, we can speculate about possible plastic changes, both structural and functional, that occur even in the axon hillock or initial segment. Structure in which sodium and potassium channels (Kv7), among others, are strategically distributed to regulate the neuron's firing. Apparently, the loss of the distance at which these channels are located from the neuronal soma could be contributing to the lack of homeostatic regulation of the intrinsic properties of neuronal excitability[30,31].

These findings are important for the scientific community since obtaining information on the mechanisms involved in epilepsy in humans is difficult for many reasons. The acquisition of epileptic tissue from patients undergoing epilepsy surgery is complicated since few hospital centers have the facilities to preserve it in good condition and then offer it for experimental studies. Therefore, scientifically, the use of animal models for experimentation is well accepted worldwide, which, from a morphological and functional point of view, shows alterations related to the pathologies that we observe in humans, such as epilepsy. These models allow us to postulate explanatory hypotheses about the neuronal mechanisms involved in epileptogenesis and the alterations it causes.

Conclusion

Neuronal excitability depends on several anatomo-functional factors, including membrane potential, ion channels, ion concentration, properties of the axon and dendrites, synapses, and neurotransmitters. The intrinsic electrical properties are controlled by several ion channels, including Kv7 channels, which are important regulators of brain function. KCNQ channels are also present in glial cells and regulate neuronal excitability by mediating the release of GABA through voltage-gated L-type Ca^{2+} channels.

Mutations in ion channels can be caused by various factors, including genetic and environmental factors, viral infections, and oxidative stress.

The SE caused by pilocarpine triggers a series of events that could increase the risk of mutations due to oxidative stress, inflammation, neuronal and glial damage[32], and various metabolic alterations. These factors could alter these channels' function, expression, or regulation, causing channelopathies, which manifest in neuronal diseases with significant morbidity. Therefore, a better understanding of the mechanism of epileptogenesis and channel opathies will lead to better design of drugs with anticonvulsant properties.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

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Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

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ORIGINAL ARTICLE

Relationship of specific language impairment with perinatal risk factors and neurological soft signs

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Abstract

Objective: *The study aimed to analyze the relationship of Specific Language Impairment (SLI) with Perinatal Risk Factors (PRFs) and Neurological Soft Signs (NSS) by sex in pre-school children.* **Methods:** *A non-experimental, transversal, comparative design with 216 girls and boys. Sociodemographic data and PRFs were documented with a Clinical History. The Screening for Language Problems was applied, and NSS were evaluated with the subtest of the Neuropsychological Battery for Pre-schoolers.* **Results:** *In 70%, the socioeconomic level was low; 51% were classified without SLI; and 27% with moderate articulation difficulties. The parents indicated that 40% had pronunciation difficulties and 71% had comprehension difficulties. A moderate significant correlation was observed with SLI and NSS: walk, asteroagnosis, and articulation difficulties.* **Conclusions:** *Screening evaluations were relevant tools to identify neurodevelopmental difficulties in pre-schoolers since they allow rapid and early attention to communication disorders, such as SLI in relation to PRFs and the presence of NSS. Furthermore, linguistic stimulation programs with extensive coverage should be undertaken in low-income communities, which were frecuent among in 70% of participants.*

Keywords: *Specific language impairment. Risk factors. Neurological soft signs. Pre-schoolers.*

Relación de los trastornos específicos de lenguaje con factores de riesgo perinatal y signos neurológicos blandos

Resumen

Objetivo: *Analizar la relación de los Trastornos Específicos de Lenguaje con los Factores de Riesgo Perinatal y los Signos Neurológicos Blandos por sexo en niños preescolares.* **Métodos:** *Diseño no experimental, transversal, comparativo con 216 niños y niñas. Se documentaron los datos sociodemográficos y de Factores de Riesgo Perinatal con una Historia Clínica. Se aplicó la evaluación Tamiz de problemas del Lenguaje (TPL) y se evaluaron los Signos Neurológicos Blandos con la subprueba de la Batería Neuropsicológica para Preescolares (BANPE).* **Resultados:** *En 70% el nivel socioeconómico fue bajo; se calificó 51% sin sospecha de Trastornos Específicos de Lenguaje; se observaron dificultades moderadas de articulación en 27%; los padres señalaron que 40% presentaban dificultades de pronunciación y 71% de comprensión. Se observó correlación significativa moderada de los Trastornos Específicos de Lenguaje con los Signos Neurológicos Blandos: marcha, asteroagnosia, y dificultades de articulación.* **Conclusiones:** *Las evaluaciones de tamizaje son herramientas relevantes para identificar dificultades del neurodesarrollo en los preescolares ya que permiten la atención rápida y temprana de los tras-*

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tornos de la comunicación, como los Trastornos Específicos del Lenguaje, los Factores de Riesgo Perinatal y los Signos Neurológicos Blandos. Además, los programas de estimulación lingüística deberían de extenderse a las comunidades de nivel socioeconómico bajo, el cual fue común en 70% de los participantes.

Palabras clave: *Trastornos específicos del lenguaje. Factores de riesgo. Signos neurológicos blandos. Preescolares.*

Introduction

In Mexico, 19.3% of children aged 24-59 months are reported to have development below the expected level for their age. Hence, it is essential to invest in educational initiatives during the initial phases[1]. According to the National Institute of Public Health[2] in the state of Sonora, México, 14.1% of boys and girls from birth to 4 years received an early childhood development evaluation.

Respecting the prevalence of language disorders, these difficulties correspond to 8.5% of boys and girls from 4 to 6 years, 11 months of age. However, in countries with fewer resources, underdiagnosis of these disorders is observed, for this reason, asking parents of children from 4 to 6 years about language acquisition, biological and environmental factors, has provided relevant information for the detection of signs of language disorders[3-5].

On the other hand, the analysis of language development difficulties has been associated with auditory processing difficulties and many cognitive processes, such as working, procedural, and declarative memories[6-8]. In contrast, language development promotes interaction, effective conflict resolution between children, self-regulation, and social and emotional skills[9].

These factors have been associated with difficulties in the development of neuropsychological processes and language of boys and girls from 3 to 6 years[10-17]. In this research examined them as Perinatal Risk Factors (PRF) and Neurological Soft Signs (NSS).

When we talk about NSS, we refer to nervous system dysfunctions due to disruptions in cortical-subcortical neuronal networks, without a specific location. NSS difficulties in the articulation and pronunciation of words were reported in 50% of Colombian children and Mexican children aged 6-11 years with low-medium socioeconomic status, oral and written language problems[18-21]. Therefore, the aim was to analyze the relationship of Specific Language Impairments (SLIs) with PRFs and NSS by sex in pre-school children.

Materials and methods

Participants

This was a non-experimental, cross-sectional, and comparative research. A sample of 216 children ranging in age from 38 to 77 months old (Mean = 60, SD = 8.1), 103 girls and 113 boys, were evaluated in 2016, in public pre-schools in the suburban areas of Xalapa, Veracruz, México.

Instruments

The clinical history of pre-schoolers was carried out, and the PRFs were documented as actual Parental perceptions of their child's: difficulties in pronunciation and comprehension. The Screening for Language Problems (TPL) and the NSS subtest of the Neuropsychological Battery for Pre-schoolers (BANPE) were applied.

PRFs documented with clinical history in pre-schoolers were birth weight, birth lenght, Apgar at 1 min and 5 min, newborn resuscitation, support of transition at birth, and in mothers were maternal age years, marital status, education, gestation time, fetal movements, threatened miscarriage, genital hemorrhage, intake of licit and illicit drugs during pregnancy, and socioeconomic status.

The TPL[22] is a screening evaluation for grammatical difficulties in children from 3 to 6 years and 11 months. It explores the language particles vulnerable in children likely to have SLI. It is done in 10 minutes on average.

The test is divided into morphology and repetition sections. In morphology, the use of articles, clitics, prepositions, and derivatives are explored; this scale consists of 13 items that are scored from 0 to 1 point; in the repetition test, 12 sentences of different complexity and length are presented and scored from 0 to 5 points depending on the sentences. TPL has a sensitivity and specificity of 0.80. The score is assigned with the percentiles of the test and is classified into three ranges according to age. In addition, the colors of the traffic light are used to indicate what was observed: no problem (green), suspected disorder (yellow), and probable disorder (red), and the percentage probability of the presence of SLI is calculated.

BANPE

BANPE[23] evaluates the normal and pathological course of the neuropsychological development of cognitive processes in pre-school, and includes tasks to evaluate 17 areas, orientation, attention and concentration,

memory, language comprehension, language expression, language articulation, motor coordination, academic skills, inhibition, working memory, flexibility, planning, abstraction, theory of mind, risk-benefit processing, emotion identification, and soft neurological signs; For this research, responses from the area of NSS were considered. In NSS, 10 areas are examined regarding the presence or absence of difficulties in language, balance, coordination, muscle tone, alternating sequences, gait, opposite finger-thumb sequences, graphesthesia, asteroagnosis, and choreiform signs.

The instrument is validated in the Mexican population, where the normalized total scores of each process have a mean of 100 and a standard deviation of 15; thus, the interpretation of the total score obtained classifies performance as: ≥ 116 high normal, 85-115 normal, 70-84 mild alteration, ≤ 69 severe alteration.

Procedure

We invited three official pre-schools from Xalapa, Veracruz, México. First, permission was requested from the school principals and children's parents. Subsequently, written informed consent was requested and obtained from all parents interested in having their children participate. All the children were evaluated with TPL and NSS, and parents answered the Clinical History.

Statistical analysis

Descriptive and inferential analysis was carried out with the JASP, 19.3.0 program. The descriptive analysis showed the distribution of cases by sex, scores on the SLI, articulation difficulties, PRF, and NSS.

In the inferential analysis, using the Kolmogorov-Smirnov test, a normal distribution of the data was observed, so in the inferential analysis, the Pearson correlation coefficient was calculated for continuous data, and the variable of SLI was correlated with NSS, PRF, and actual parental perceptions of their language child's.

The correlation values considered were ≤ 0.09, null; from 0.10 to 0.29, weak; 0.30 to 0.49, moderate, and 0.50 to 1, strong[24]. The distribution of SLI due to articulation difficulties was compared with the Chi-square test.

Results

From the data, 47% of pre-schoolers were 60-71 months old; 55% were full-term birth, Apgar at 1 and 5 min were from 8 to 10, none required newborn resuscitation, even support of transition at birth. Regarding the mother's average age was 29 years, 15% had threatened miscarriage, 37% were not married, 28% were married, genital hemorrhage, 72% had no genital hemorrhage, 125 minimal and none reported intake of licit and illicit drugs during pregnancy and 70% had a low socioeconomic level.

Regarding language, 51% of pre-schoolers have no SLI; about NSS in March 38% present difficulties, in coordination 63% and 27% had moderate articulation difficulties. The parents' report indicated that 40% had pronunciation difficulties and 71% had comprehension difficulties (Table 1). In the distribution of participants by SLI and sex, we observed that 49% of boys and 53% of girls did not present SLI, while 31% of boys and 25% of girls present suspected SLI, and 20% had a probable SLI in boys and in girls 22% (Fig. 1). When performing the Pearson correlation coefficient of SLI with PRF were not statistically significant correlations while with NSS, we observed a significant moderate correlation with articulation difficulties ($r = 0.311$, $p = 0.001$); and weak correlation with asteroagnosis ($r = 0.289$, $p = 0.001$), and March ($r = 0.282$, $p = 0.001$) (Table 2). When comparing Morphology and Sentence Repetition, we observed significant moderate correlations of asteroagnosis ($r = -0.353$, $p = 0.001$), and articulation difficulties ($r = -0.414$, $p = 0.001$). Regarding sentence repetition, there were significant moderate correlations with March ($r = -367$, $p = 0.001$), asteroagnosis ($r = -0.433$, $p = 0.001$), and articulation difficulties ($r = -0.380$, $p = 0.001$) (Table 3).

Correlations between Morphology with SNB agreed to had no difficulties in March 64%, coordination 53%, asteroagnosis 63%, and articulation difficulties 40%, while Repetition of sentences in March 83%, coordination 72%, asteroagnosis 83%, and articulation difficulties 47% (Table 4).

Regarding comparison of the SLI and articulation difficulties, both instruments agreed that 23% had no problems, 6% had mild, and 9-13% had moderate to severe difficulties ($\chi^2 = 28.086$, $p = 0.001$) (Table 5).

Discussion

Many difficulties in early childhood development as language were observed upon returning to school following the pandemic, because of conditions in which children continued school learning from their homes. For that reason, the communication disorders in Mexican pre-schools were the focus of this analysis[21,25,26].

In this research, we analyze data collected in evaluations before the COVID-19 pandemic period, where

Table 1. Descriptive variables of the sample

Variables	Criteria	Frequency	%
Children's data			
Age (months)	38-47	18	8
	48-59	79	37
	60-71	102	47
	72-77	17	8
Sex	Female	103	48
	Male	113	52
Specific language impairment	Absent	110	51
	Suspect	61	28
	Probable	45	20
Neurological soft signs			
March	Present	83	38
	Absent	132	61
Coordination	Present	136	63
	Absent	79	36
Asteroagnosis	Present	51	24
	Absent	164	76
Articulation difficulties	Absent	74	34
	Mild	30	14
	Moderate	59	27
	Severe	51	24
	No data	2	1
Mother's data			
Perinatal risk factors			
Gestation time	No data	47	21
	Ful term	118	55
	Preterm	51	24
Socioeconomic level	Low	152	70
	Medium	33	15
	No data	31	14
Parental perceptions of their child's			
Pronunciation difficulties	Present	86	40
	Absent	93	43
	No data	37	17
Comprehension difficulties	Present	154	71
	Absent	20	9
	No data	42	19

Table 2. Correlations of specific language impairment with neurological soft signs

Variables	Correlation	p
March	0.282	< 0.001
Coordination	0.064	0.352
Asteroagnosis	0.289	< 0.001
Articulation difficulties	0.311	< 0.001

Table 3. Correlations of morphology and sentence repetition with neurological soft signs

Variables	Morphology		Repetition	
	Correlation	p	Correlation	p
March	–0.323	< 0.001	–0.367	< 0.001
Coordination	–0.060	0.385	–0.041	0.547
Asteroagnosis	–0.353	< 0.001	–0.433	< 0.001
Articulation difficulties	–0.414	< 0.001	–0.380	< 0.001

Table 4. Percentage of morphology and sentences repetition and neurological soft signs

Variables	Morphology (%)		Sentences repetition (%)	
	Absent	Present	Absent	Present
March	64	7	83	5
Coordination	53	6	72	4
Asteroagnosis	63	7	83	5
Articulation difficulties	40	25	47	10

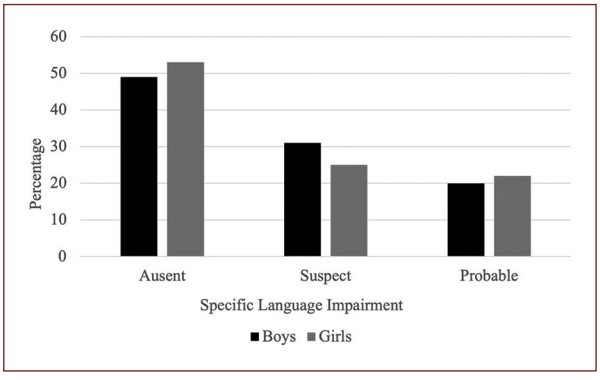

Figure 1. Percentage of children by language disorder and sex.

Table 5. Comparison of specific language impairment and articulation difficulties in pre-schoolers

Specific language impairment	Articulation difficulties (%)				Total (%)
	Ausent	Mild	Moderate	Severe	
Absent	49 (23)	13 (6)	28 (13)	18 (9)	108 (51)
Suspect	20 (9)	12 (6)	18 (9)	11 (5)	61 (29)
Probable	5 (2)	5 (2)	13 (6)	22 (10)	45 (20)
Total	74 (35)	30 (14)	59 (28)	51 (24)	214 (100)

$\chi^2 = 28.086$, $p = 0.001$.

we observed that a suspected or probable SLI was observed in 51% of pre-school boys and girls and 67% of articulation disorders, therefore that diagnostic evaluations are required to differentiate what is the primary difficulty in these cases because language is learning predictor of the acquisition of reading and writing, as mentioned by Bonifacci et al.[27,28], who found significant associations between language comprehension and reading comprehension; as well as between the morphosyntactic structures of the language with the reading speed in bilingual children who speak Italian and French.

Relevantly, we recommended diagnostic language assessments for the children we identified as having severe articulating difficulties and probable language abnormalities so that the specific communication impairment they presented could be determined. In this context, Georgan et al.[29] highlights the importance of determining whether linguistic traits are indicative of certain language disorders or articulation issues since this would have varying effects on academic performance and necessitate the provision of early help suitable for each condition.

About PRF, it is known that the presence of social and neurobiological risk factors from 22 weeks gestation to 7 days after birth has been shown to affect language, motor, and social development. Among these factors have been reported in children: Peri-intraventricular hemorrhage or bronchopulmonary, birth weight less than 1000g, and long hospital stay, and in mothers, maternal age < 18% and 70% had low socioeconomic level[13,30-32].

In this research, PRF documented with parental perceptions of their child's, this was a limitation because we did not have imaging or electrophysiological testing to confirm the presence of any neurological impairment related to language difficulties. However, in this research, we use standardized screening assessments as a first level in language difficulty detection[33]. Then we assigned children with suspected SLI and Articulation difficulties to diagnostic assessments to determine the certainty of findings and situable intervention.

Although we found no significant correlations between socioeconomic level, SLI, and articulation difficulties, there have been reports of the impact of poverty levels in poor communicative interactions since stimulation in those contexts is tipically limited[34,35].

In other studies about perception´s parents emphasize the importance to parental involvement in the assessment process because parents recognize the relevance to seeing the child's reactions, perceiving other aspects about their child´s development, and have a deeper understanding about child's problems[36]. We did not capture this component of the study, despite the fact that the child's parents were present for the assessments. Even though no correlations were observed between PRF and SLI, we can point out that 49% of pre-schoolers with suspected or probable SLI are considered to have delays in neuromaturational development, as pointed out by Rincon-Lozada et al.[20]. Therefore, timely follow-up and attention must be given, about which we cannot give any information, because results were delivered to the parents with suggestions for support and recommendations for care with language development professionals at the Rehabilitation and Social Center Inclusion of Veracruz, CRISVER, or with the support teachers of the Psychopedagogical Care Center for Pre-school Education, CAPEP. Although the significant correlations found between SLI and NSS were moderate, it is relevant to consider that NSS corresponded to difficulties in walking and articulation. Regarding risk factors, Chumacero-Calle et al.[18], and Rincon-Lozada et al.[20], mention that Colombian children of medium to low socioeconomic level, as in the case of the children evaluated in our research, encountered difficulties in language and writing, however, we

did not find significant correlations because it was a common condition in the majority of the pre-school families, with 70% at a low level and 14% at a medium level, with 15% without reporting the data. We thought to examine whether the TPL instrument's subtests revealed any associations with PRF and NSS and we observed de similar correlations with SLI; however, a higher percentage of children had difficulties in Morphology than in Sentence Repetition. On the other hand, although we did not find correlations with parental perceptions of their children about comprehension and expression language, these observations favored applying standardized screening instruments as the first level of evaluation. Regarding parental perceptions of their children, the findings of Auza et al.[3,4], mentioned that in low-income populations lacking access to evaluations like we conducted, parents' reports about their children's development are a crucial source of information for implementing intervention actions in addition to making reasonable adjustments in educational programs.

It was important to know in what percentage two variables coincided to find the presence or absence from difficulties. That's why, we observed that three NSS with SLI agreed that 23% did not present difficulties, while in articulation, 38% presented moderate or severe difficulties and suspected or probable SLI. It is important to increase the dissemination of SLI screening so that families have knowledge of it and will be detected earlier more children. It was necessary to determine whether difficulties observed in the pre-schoolers corresponded to the phonological disorders identified through the evaluation of NSS or to the SLI identified with TPL, or if there were pre-schoolers who presented both difficulties. Communication disorders are defined as language, phonological, verbal fluency, and pragmatic communication disorders in the Diagnostic and Statistical Manual of Mental Disorders[37]. In the two assessments that were conducted, we discovered that 23% of the pre-schoolers did not exhibit communication problems, 11% had grammar issues, and 28% had articulation issues. It was decided that 15% of respondents had moderate issues and 15% had severe difficulties when it came to the presence of both. In addition to directing parents and educators, the analysis allowed the suggestion of diagnostic tests to be carried out in severe situations with the purpose to confirm or not the indicators observed.

By considering the parameters, we were able to achieve the intended goal of examining the correlation between SLI with NSS in pre-schoolers. We discovered that the percentages were higher than those reported by Vázquez-Salas et al.[1]. However, as already mentioned, we did not follow-up how many children with severe problems were evaluated with diagnostic instruments and we also did not follow-up the subsequent children's development.

Conclusions

Since standardized screening evaluations permit rapid attention to communication disorders, such as SLI in relation to PRF and the presence of NSS, which are the guiding variables of this study, they are appropriate instruments to identify neurodevelopmental difficulties in pre-schoolers. Pre-schoolers' development should be closely monitored to prevent deficits in basic competencies, such as writing, reading, and logical math concepts. Furthermore, linguistic stimulation programs with extensive coverage should be undertaken in low-income communities, which are frecuent among in most participants.

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Conflicts of interest

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REVIEW ARTICLE

Alterations of the GABAergic system in binge eating disorder: a systematic review

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Abstract

Binge eating disorder (BED) is characterized by recurrent episodes of excessive intake within a limited time period, accompanied by loss of control and distress. These behaviors may overstimulate and desensitize the dopaminergic system, leading to the search for palatable foods to reactivate a hypofunctional reward circuit. Dopamine release activates GABAergic pathways, which exert inhibitory control by reducing dopamine release, suggesting that this system may be altered in the context of BED. The objective of this systematic review was to gather research conducted between 2013 and 2023 on GABAergic functioning in eating behavior and binge episodes, focusing exclusively on rodent models (rats and mice). The review followed PRISMA 2020 guidelines, using ScienceDirect and PubMed as data sources. The initial search yielded 488 results. After screening, 23 articles were selected, and five met the inclusion criteria. Of these, 60% (n = 3) were conducted in mice and 40% (n = 2) in rats. In 80% of cases (n = 4), only male animals were used, while 20% (n = 1) included both sexes. Likewise, 80% (n = 4) used adult animals, and 20% (n = 1) did not report age. Contradictory results emerged regarding GABA involvement in feeding behavior: some studies showed increased intake associated with both lower and higher GABAergic activation, while others reported the opposite pattern. These inconsistencies may reflect interactions between distinct neuroanatomical regions and procedural differences. Most studies focused on general food intake modulation rather than binge-specific behaviors, limiting the direct applicability of findings to BED.

Keywords: *Binge eating disorder. GABAergic system. Dopaminergic system. Neurobiological mechanisms. Eating behavior.*

Alteraciones del sistema GABAérgico en el trastorno por atracón: una revisión sistemática

Resumen

El Trastorno por Atracón se caracteriza por episodios recurrentes de ingesta excesiva en un período de tiempo limitado, acompañados por pérdida de control y malestar significativo. Estos episodios pueden generar sobreestimulación y posterior desensibilización del sistema dopaminérgico, favoreciendo la búsqueda de alimentos palatables para reactivar un sistema de recompensa hipofuncional. La liberación de dopamina activa vías GABAérgicas inhibidoras que reducen su propia liberación, lo que sugiere posibles alteraciones en este sistema. El objetivo de esta revisión sistemática fue recopilar investigaciones realizadas entre 2013 y 2023 sobre el funcionamiento GABAérgico en la conducta alimentaria y en episodios de

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atracón. Se consideraron únicamente estudios en modelos animales (ratas o ratones). Se siguieron las directrices de PRISMA 2020, utilizando ScienceDirect y PubMed. La búsqueda inicial arrojó 488 resultados; tras la selección, 23 artículos fueron evaluados y 5 cumplieron con los criterios de inclusión. De ellos, el 60% (n = 3) se realizó en ratones y el 40% (n = 2) en ratas. En el 80% (n = 4) se utilizaron machos y en el 20% (n = 1) ambos sexos. El 80% (n = 4) empleó animales adultos y uno no informó la edad. Se identificaron resultados contradictorios: algunos estudios mostraron mayor ingesta con menor o mayor activación GABAérgica, mientras que otros evidenciaron el patrón inverso. Esta ambigüedad podría deberse a diferencias neuroanatómicas y metodológicas. La mayoría abordó la modulación general de la ingesta, lo que limita la extrapolación directa de los hallazgos al fenotipo conductual del trastorno por atracón.

Palabras clave: *Trastorno por atracón. Sistema GABAérgico. Sistema dopaminérgico. Mecanismos neurobiológicos. Conducta alimentaria.*

Introduction

Binge eating disorder (BED) is characterized by recurrent episodes of excessive intake, within a limited time, of an amount of food that is larger than what most individuals would consume in a comparable period. These episodes are accompanied by a sense of loss of control over food intake, leading to significant distress regarding the binge eating. These episodes occur on average at least once a week for 3 months and are associated with at least three of the following symptoms and signs: eating much more rapidly than normal, eating until feeling uncomfortably full, consuming large amounts of food when not physically hungry, eating alone due to feeling ashamed about the amount of food being eaten, and feeling disgusted with oneself, depressed, or very ashamed following the binge eating[1].

Changes in eating behavior may be related to variations in neurochemical components. Several studies suggest that the neurobiological mechanisms involved in binge eating episodes are primarily associated with the dopaminergic system[2-4]. However, the literature presents contradictory and ambiguous findings. Some studies, conducted in both humans and animals, report hyperactivation of the system[5-11] whereas others observe hypoactivation[7,12-21]. One possible explanation is that these hyperdopaminergic and hypodopaminergic states are not mutually exclusive but may occur at different stages of binge eating. Dopamine elevations could contribute to the initiation of binge eating behavior, followed by downregulation after a sustained pattern of overconsumption is established[22]. Taken together, these results suggest that binge eating episodes would generate overstimulation and, ultimately, desensitization of the mesocorticolimbic dopamine system as the main reward circuit[3,23,24]. Consequently, the overconsumption of appetitive stimuli could reflect the need to reactivate a hypofunctional reward circuit[11,25]. In this regard, treatments with dopaminergic agonists, such as lisdexamfetamine, improve dopaminergic and noradrenergic neurotransmission[26,27] and reduce episodes of overconsumption in both rats[28,29] and humans[30].

On the other hand, the hypofunction of the dopaminergic system in advanced stages of BED could depend on increased activation of the GABAergic system. Dopamine release activates GABAergic pathways, which act as inhibitors by reducing dopamine release. This regulation by the GABAergic system allows for maintaining a balance in the reward circuit and preventing dopamine overload[31,32].

Gamma-aminobutyric acid (GABA) is the principal inhibitory neurotransmitter of the central nervous system and plays multiple roles in both neuronal and non-neuronal tissues. Its synthesis primarily derives from glucose, which is metabolized into glutamate through enzymes of the tricarboxylic acid cycle. The enzyme glutamic acid decarboxylase (GAD), predominantly expressed in GABAergic neurons, catalyzes the decarboxylation of glutamate to produce GABA. Once synthesized, GABA is transported into synaptic vesicles through the vesicular GABA transporter. Subsequently, calcium influx into the presynaptic terminal triggers exocytosis. This cellular process involves the fusion of intracellular vesicle membranes with the plasma membrane, releasing their contents into the extracellular space. It is an energy-consuming active transport pathway utilized by cells to release GABA into the synaptic cleft[33].

Their function is modulated by ionotropic ($GABA_A$ and $GABA_C$) and metabotropic ($GABA_B$) receptors located on the postsynaptic neuron. Ionotropic receptors are coupled to chloride channels, implying synaptic transmission with lower metabolic expenditure and faster kinetics. In contrast, metabotropic receptors entail additional energy expenditure to perform their function. These receptors are coupled to a G protein (GPCR) and are separated from the ion channel, enabling them to modulate inhibitory transmission that is slower but also more prolonged[34,35].

On completion of GABA action on receptors, it is cleared from the synaptic cleft. The mechanism of GABA clearance begins with its reuptake through GABA transporters (GAT), membrane proteins located in presynaptic terminals. The enzyme GABA transaminase (GABA-T) catalyzes the conversion of GABA to succinic semialdehyde. Subsequently, succinic semialdehyde is converted to succinate by the enzyme succinic semialdehyde dehydrogenase. However, not all GABA is converted to succinate; a portion is also recycled for the synthesis of new GABA[33].

At the presynaptic terminal, metabotropic receptors CB1, also known as type 1 cannabinoid receptors, are located. These receptors interact with anandamide, an endocannabinoid released by the postsynaptic neuron on depolarization. This interaction leads to the modulation of neuronal activity and causes a decrease in neurotransmitter release[36].

Furthermore, GABA plays a fundamental role in neuronal function by regulating neuron excitability and dopamine release. The latter is closely linked to various functions such as motor activity regulation, attention, learning, wanting, and the reward system, among other functions[37].

Dopamine synthesis begins with the action of tyrosine hydroxylase, a key enzyme in the biosynthesis of neurotransmitters dopamine, noradrenaline, and adrenaline. This enzyme catalyzes the conversion of the amino acid L-tyrosine into 3,4-dihydroxyphenylalanine (L-DOPA). Subsequently, L-DOPA is transformed into dopamine through the action of the enzyme dopa decarboxylase. Once released into the synaptic cleft, dopamine exerts its effects primarily by stimulating metabotropic dopamine receptors. These receptors are subdivided into different subtypes, including D_1-like receptors (D_1 and D5) and D_2-like receptors (D_2, D_3, and D_4), among others. After fulfilling its function, dopamine is reuptaken by the presynaptic neuron through dopamine transporters known as DAT. Once taken back up, dopamine is metabolized by the enzyme monoamine oxidase in a degradation process[38]. It is crucial to note that the information provided above is a general outline of the synthesis, action, and elimination processes of dopamine and GABA. However, it is important to highlight that there are other factors and pathways also involved in the metabolism and elimination of these neurotransmitters.

The general objective was to conduct a systematic review to gather research conducted from 2013 to 2023 on the functioning of the GABAergic system in eating behavior and binge eating episodes. It is important to acknowledge that, although validated animal models of BED are available, preclinical studies specifically examining the GABAergic system in BED remain relatively scarce. Consequently, most available studies have focused on general modulation of food intake or overeating behaviors, which may not fully capture the core behavioral phenotype characteristic of BED. This limitation affects the breadth and translational relevance of current evidence regarding the role of the GABAergic system in BED. Therefore, while this review includes studies addressing excessive eating behavior broadly, caution is warranted in extrapolating findings directly to BED.

The review will be exclusively limited to studies using animal models (i.e., rats or mice), as these are a valuable tool for addressing hypotheses about the neurobiological mechanisms of ingestion behavior.

General methodology

Eligibility criteria

The review is based on the guidelines proposed by the PRISMA 2020 methodology for reporting systematic reviews[39]. This methodology involves establishing the selection criteria for the studies to be included. Research published between 2013 and 2023, reported in articles published in English-language journals, was considered.

We included preclinical studies using rodent models (rats or mice) that assessed the GABAergic system in the context of excessive eating behavior. Eligible studies did not have to model BED explicitly, but were required to examine behaviors operationally defined as binge-like eating or overeating, such as the consumption of large quantities of palatable food in a short period, independent of food deprivation status. Studies had to provide neurobiological data related to the GABAergic system (e.g., receptor expression, pharmacological modulation, or GABA-related gene expression).

Sources of information

The databases ScienceDirect and PubMed were utilized, incorporating the combination of the following keywords in English: (((binge-like eating episodes) OR (binge-eating episodes) OR (overeating)) AND (GABAergic system) AND (rat OR mice)). To ensure literature saturation, forward search strategies (searching for articles citing the included study) and backward search strategies (reviewing the reference lists of included studies) were applied. In addition, the reference lists of

systematic reviews and meta-analyses on the topic were reviewed.

General procedure

Identification

The initial search was conducted on March 22, 2023. This identified 488 records across the two databases used: ScienceDirect (n = 480) and PubMed (n = 8; Fig. 1).

Screening

During screening, the number of records was reduced to 23. Articles were excluded (n = 465) based on title screening, as they did not study the relationship between the GABAergic system and feeding regulation.

Suitability

The process of reviewing abstracts of selected articles was conducted. Out of the 23 articles initially considered for eligibility, retrieving 11 articles was requested. On suitability analysis, the number of articles reduced to 5 as they met all inclusion criteria: being published between 2013 and 2023, using animal models of rats or mice, and being empirical research on the relationship between the GABAergic system and binge-eating episodes.

Included

The full-text reading of the selected studies was conducted during suitability assessment. All articles analyzed for eligibility were selected for the systematic review (n = 5).

Analysis

During the review of each article, the following information was examined: the names of the study authors, the journal, and the year of publication. In addition, the objectives, sample, experimental design, measures used, and results were analyzed.

Risk of bias (RoB) assessment

The methodological quality of the included preclinical studies was evaluated using the SYRCLE's RoB tool, which is specifically adapted for animal research. This tool assesses ten key domains:

1. Random sequence generation
2. Baseline group similarity
3. Allocation concealment (housing randomization)
4. Blinding of caregivers
5. Blinding during intervention administration
6. Blinding of outcome assessment
7. Randomization in data/sample analysis
8. Incomplete outcome data (attrition)
9. Selective outcome reporting
10. Other sources of bias (e.g., ethics and conflicts of interest).

Two independent reviewers assessed each domain and classified it as: low risk (clear adherence to the criterion), high risk (criterion not met), and unclear risk (insufficient information). Discrepancies (< 5% of cases) were resolved by consensus or through consultation with a third reviewer.

Assessment results

Eighty percentages of the studies showed low RoB in initial randomization (domain 1), and all studies adequately reported outcome data (domain 8) and declared no conflicts of interest (domain 10), which represent notable methodological strengths. However, all studies presented high risk in the domain related to blinding during intervention administration (domain 5), and 60% showed unclear risk regarding housing randomization (domain 3). These findings suggest that, while the included studies maintained acceptable standards in randomization and transparency, the consistent lack of blinding in intervention delivery may have introduced performance bias. This common limitation in preclinical research highlights the need for cautious interpretation of the observed effects.

Results

The initial search identified 488 results, of which 480 were found in the ScienceDirect database and eight in PubMed. During screening, the number was reduced to 23 articles, of which only five were deemed suitable for this study (Fig. 1). Of the five reviewed studies, 60% (n = 3) were conducted in mice and 40% (n = 2) in rats. In 80% (n = 4) of the studies, only male animals were used, and in the remaining 20% (n = 1), both males and females were used, with no studies exclusively focusing on females. Regarding age, 80% (n = 4) of the articles used adult animals, and 20% (n = 1) did not specify the age (Table 1).

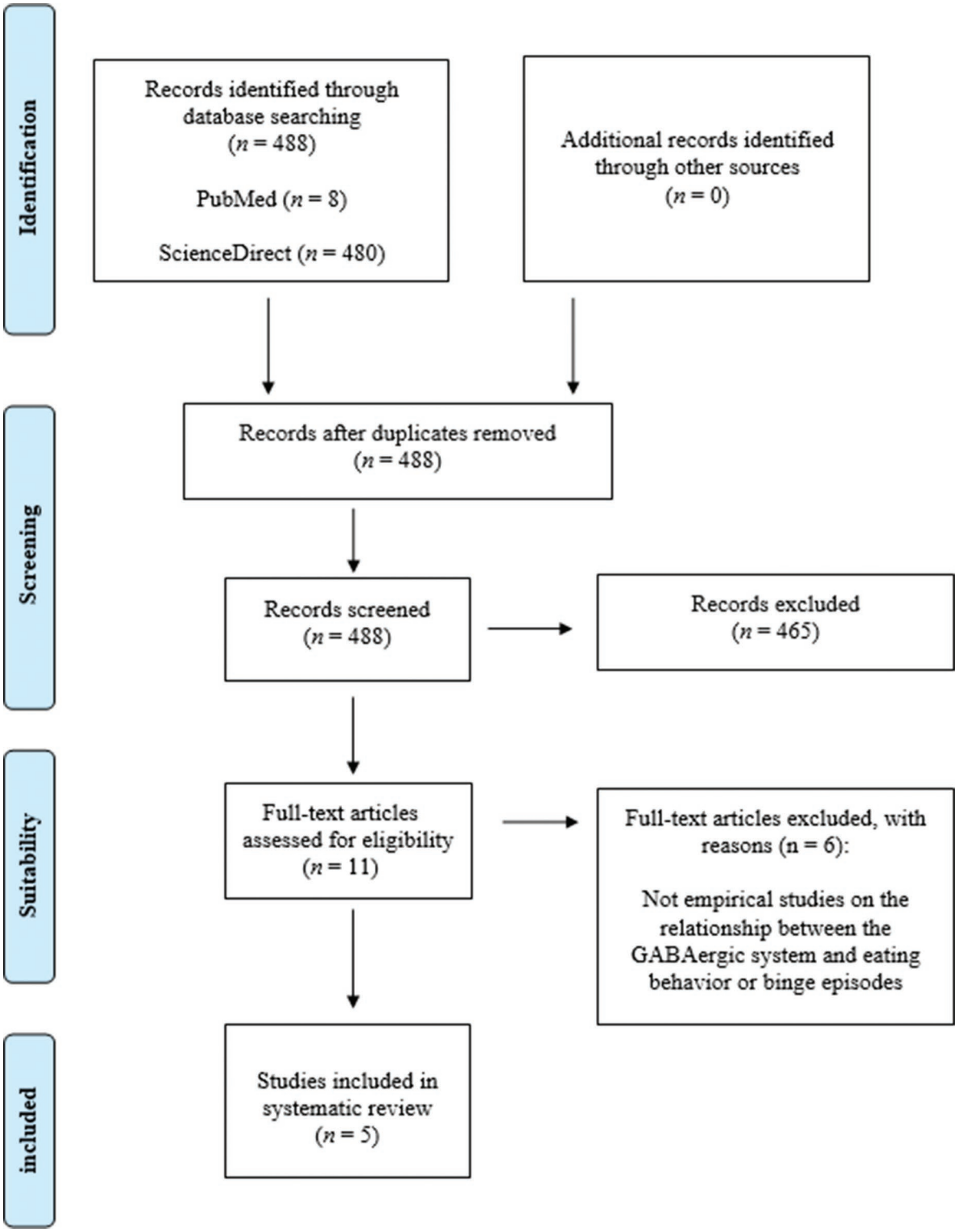

Figure 1. Flowchart of literature search according to PRISMA.

Binge eating model

Of the five studies reviewed in this work, only one used a behavioral model to generate binge eating episodes[14], while the remaining studies directly intervened in the GABAergic pathways to influence intake. In the study by Corwin et al.[14], animals were assigned to one of two conditions, counterbalancing their body weight. One group was exposed to vegetable fat for 1 h on alternate days (INT group), while the other group was exposed to it daily (D group). Both groups were provided with water and balanced food throughout the procedure. The experimental protocol lasted 5-8 weeks. It was observed that binge eating episodes occurred in the intermittent condition during the presentation of highly palatable food.

Intervention procedures in GABA

The experiments conducted by Corwin et al.[14] aimed to evaluate gene expression within the ventral tegmental area (VTA) and the prefrontal cortex (PFC) in rats with binge-eating episodes (INT) and control rats (D), 20 min before and 20 min after the presentation of palatable food. The intervention procedure on the GABAergic pathways consisted of administrations of muscimol/baclofen, two agonists that act on GABAergic receptors. Muscimol interacts with both $GABA_A$ and $GABA_B$ receptors, while baclofen selectively affects $GABA_B$ receptors. Both drugs were injected locally into the dorsomedial (n = 18) and ventromedial (n = 14) PFC. The dependent variables were the intake of vegetable fat in grams (g) over 1 h, and the mRNA expression for $GABA_A$ and $GABA_B$ receptors.

In both the study by Hao et al.[40] and Marino et al.[41], GABAergic pathways were intervened using optogenetic techniques. This is a genetic engineering technique involving the introduction of opsins into neurons. Opsins are light-sensitive proteins obtained from photosynthetic microorganisms that have the ability to convert light energy into electrical signals within nerve cells. These proteins can function as ion channels or pumps, meaning they allow the flow of ions across the cell membrane in response to light, modulating neuronal activity by either activating or inhibiting it[42].

The experiments conducted by Hao et al.[40] used adult male mice (2-4 months old) from the Gad2-ires-Cre strain (JAX nº 019022) and C57BL/6J strain. The intervention procedure on the GABAergic pathways consisted of pharmacological and optogenetic techniques. The first involved administering an injection of muscimol (n = 7), a selective $GABA_A$ receptor agonist, or saline (n = 7) into the anterior ventrolateral periaqueductal gray (vlPAG) of C57BL/6J mice. The dependent variables were food intake in grams (g), the number of approaches to food, and feeding latency in seconds (s). The second technique involved incorporating halorhodopsin (NpHR; n = 8) and channelrhodopsin (ChR2; n = 7) opsins into GABAergic neurons of the same region in Gad2-ires-Cre mice. ChR2 opsin functions as a light-sensitive ion channel, allowing the influx of sodium (Na^+) or calcium ions (Ca^{2+}) into the cell, leading to increased activity in GABAergic neural pathways. On the other hand, when NpHR opsin is expressed in GABAergic neurons, exposure to light allows the influx of chloride ions (Cl^-) into the cell, resulting in hyperpolarization and consequently reducing neurotransmitter release and GABAergic signal transmission. Finally, a yellow fluorescent protein (eYFP; n = 8), which did not include any opsins, was incorporated into the control condition. The dependent variables were food intake in grams (g), the number of approaches to food, and the total time spent feeding in seconds (s).

In the study by Marino et al.[41], male and female transgenic mice expressing ChR2 in GABAergic projections from the lateral hypothalamus (LH) to the VTA were used. The mice (n = 8) were non-food deprived and were between 10 and 20 weeks old at the time of surgery. The dependent variable was the feeding time in seconds (s) in response to optogenetic inhibition or stimulation (5, 10, 20, and 40 Hz) for 1 min.

On the other hand, the experiments by Cruz-Martínez et al.[43] intervened in the GABAergic system through the activation of CB1 receptors in the paraventricular nucleus (PVN) of the hypothalamus (PVN). Male Wistar rats were used, with 21 h of food deprivation before the trial.

ACEA (a CB1 agonist) and AM 251 (a CB1 antagonist) were injected into this brain region, and the release of GABA was evaluated. The animals were divided into four groups: intra-PVN injected with ACEA (n = 8), AM 251 (n = 5), a combination of both drugs (n = 6), or vehicle (n = 8). Subsequently, food intake in grams (g) and the release of [3H] GABA were assessed during the following 2 h.

The study conducted by Sato et al.[44] aimed to delve into the mechanisms underlying the decrease in body weight induced by dietary GABA administration. In Experiment 1, diets containing varying levels of GABA were provided over a period of 2 weeks: 0% (0 g; n = 8), 0.5% (5 g; n = 8), 2% (20 g; n = 8), and 5% (50 g; n = 8). In Experiment 2, subcutaneous injections of vigabatrin,

Table 1. Studies reporting GABAergic alterations.

Authors	Study objective	Methodology	Main results
Hao et al.[40]	To evaluate the role of GABAergic cells in the anterior ventrolateral periaqueductal gray (vlPAG) on the regulation of feeding behavior.	Adult male mice (2-4 months old) from the Gad2-ires-Cre and C57BL/6J strains were utilized for the study. The intervention involved both pharmacological and optogenetic techniques. The first technique entailed the administration of muscimol (n = 7) or saline (n = 7) into the anterior vlPAG of C57BL/6J mice without food deprivation. The second technique involved the incorporation of halorhodopsin (NpHR; n = 8) and Channelrhodopsin (ChR2; n = 7) into GABAergic neurons of the same region in Gad2-ires-Cre mice, both with and without food deprivation. Dependent variables included food intake (g) over 30 or 60 min, feeding latency (s), number of approaches to food, and total feeding time (s) over 10 min	The results demonstrate that the suppression of activity of GABAergic cells in the anterior vlPAG, both directly and through their inputs from the lateral hypothalamus (LH) and bed nucleus of the stria terminalis, promotes feeding in satiated mice. Conversely, activation of these cells disrupts food intake in food-deprived mice.
Marino et al.[41]	Characterize the neural circuits involved in compulsive eating.	Male and female transgenic mice expressing ChR2 in GABAergic projections from the LH to the ventral tegmental area (VTA) were used. The mice (n = 8) were food-satiated and aged between 10 and 20 weeks at the time of surgery. The dependent variable was the feeding time (s) under optogenetic inhibition or stimulation (5, 10, 20, and 40 Hz) for 1 min.	The data indicate that peripheral GABA neurons in the locus coeruleus (LC) are a critical step in the descending circuit for LH neurons, whereas GABA neurons in the VTA are not. Activation of this LH-peri-LC pathway would be necessary and sufficient to induce overeating in satiated mice.
Cruz-Martínez et al.[43]	Characterize the neurochemical mechanisms related to the hyperphagic effects induced by the activation of CB1 receptors in the paraventricular nucleus of the hypothalamus (PVN)	Male Wistar rats with 21 h of food deprivation before the trial were used. The animals were divided into 4 groups and injected intra-PVN with saline solution (n = 8), ACEA (n = 8), AM 251 (n = 5), and ACEA+AM251 (n = 6). Dependent variables were: food intake in grams (g) and the release of [3H] GABA over a period of 2 h.	The findings suggest that the observed increase in food intake is more strongly associated with GABAergic hyperfunction in the PVN rather than hypofunction.
Corwin et al.[14]	To evaluate gene expression within the VTA and prefrontal cortex (PFC) in rats experiencing binge-eating episodes (INT) and control rats (D), 20 min before and 20 min after presentation of palatable food.	Male Sprague-Dawley rats (60 days old) were used. One group was exposed to vegetable fat for 1 h on alternate days (INT), while the other group received it daily (D). The intervention procedure on GABAergic pathways consisted of administrations of muscimol/baclofen, which were locally infused into the dorsomedial (n = 18) and ventromedial (n = 14) PFC. Dependent variables were vegetable fat intake (g) over one hour and mRNA expression for $GABA_A$ and $GABA_B$ receptors.	The findings suggest that initially, binge-eating episodes would lead to an increase in dopaminergic activity, and if this behavior persists over time, it would result in an increase in GABAergic activity to decrease dopaminergic activity.
Sato et al.[44]	Evaluate the underlying mechanisms of the decrease in body weight generated by the addition of GABA to the supplied food.	In experiment 1, diets containing variable levels of GABA were supplied over a period of 2 weeks: 0% (0 g; n = 8), 0.5% (5 g; n = 8), 2% (20 g; n = 8), and 5% (50 g; n = 8). In experiment 2, subcutaneous injections of vigabatrin, a GABA-degrading enzyme inhibitor (GABA-T), were administered daily to mice receiving diets with 0.5% and 2% GABA. Dependent variables were: intake of balanced food (grams/6 weeks), body weight (grams/6 weeks), and plasma GABA levels (μM) and hippocampal GABA levels (μmol/g).	The findings suggest that increasing GABA levels in the central nervous system can significantly decrease both food intake and body weight.

a GABA transaminase (GABA-T) enzyme inhibitor, were administered daily to mice receiving diets with 0.5% and 2% GABA. The experimental conditions were as follows: 0% + saline (n = 6), 0.5% + saline (n = 6), and 2% + saline (n = 6), 0.5% + vigabatrin (n = 6), and 2% + vigabatrin (n = 6). The dependent variables included intake of balanced food (grams/6 weeks), body weight (grams/6 weeks), and levels of GABA in plasma (μM) and GABA in the hippocampus (μmol/g).

Alterations in the GABAergic system

The pharmacological studies by Hao et al.[40] found that muscimol injection led to an exacerbation of food intake and the number of approaches to food, along with a decrease in feeding latency compared to the saline group. On the other hand, in the optogenetic studies, the ChR2 condition showed a decrease in food intake, the number of approaches to food, and the total time spent feeding compared to the control condition eYFP. In the NpHR condition, an increase in food intake, the number of approaches to food, and the total time spent feeding was observed compared to the control condition eYFP.

This suggests that GABAergic cells in the anterior part of the vlPAG play a central role in the regulation of feeding. This structure receives direct inputs from many nuclei related to feeding: the LH, the bed nucleus of the stria terminalis (BNST), the central amygdala nucleus (CeA), the arcuate nucleus (ARC), the PVN of the hypothalamus, and the dorsal raphe nucleus (DR). When examining the LH_{GABA}-vlPAG, $BNST_{GABA}$-vlPAG, and CeA_{GABA}-vlPAG pathways, the study found that the suppression of the first two pathways separately was sufficient to induce overeating in sated mice, while optogenetic activation of the CeA_{GABA}-vlPAG pathway did not induce significant behavioral changes. In addition, activation of the LH_{GABA}-vlPAG and $BNST_{GABA}$-vlPAG pathways separately resulted in a significant reduction in consumption in food-deprived mice.

In the study by Marino et al.[41], a series of experiments were conducted to delineate the neuronal circuitry involved in overeating episodes in satiated mice. The authors hypothesized that stimulation of GABAergic projections from the LH to the VTA could lead to overeating. In addition, they expected strong rostral projections to anterior BNST, the dentate gyrus, and the lateral habenula. Caudal projections extended to and through the VTA and the rostromedial tegmental nucleus, which then branched dorsally toward the locus coeruleus (LC) and ventrally toward the dorsal inferior olive.

However, only photostimulation of VTA projections to the peri-LC induced overeating, while other brain regions either did not produce feeding or their effects did not reach statistical significance. On the other hand, to determine if GABAergic neurons in the LC are linked to overeating induced by LH, GABAergic neurons in the LC and VTA were photoinhibited. The authors observed that photoinhibition of GABAergic neurons in the LC and photostimulation of LH disrupted feeding behavior, while photoinhibition of GABAergic neurons in the VTA and photostimulation of LH led to overeating. These data suggest that GABAergic neurons in the LC are a critical step in the descending circuit for LH neurons, whereas GABAergic neurons in the VTA are not. Activation of this LH-LC pathway would be necessary and sufficient to induce overeating in satiated mice.

Cruz-Martínez et al.[43] aimed to characterize the neurochemical mechanisms related to hyperphagic effects induced by CB1 receptor activation in the PVN. Since cannabinoid-induced hyperphagia can be triggered by inhibition of satiety and/or stimulation of orexigenic signals, the hypothesis was raised that CB1 receptor activation in the hypothalamus could induce changes in GABA release.

The results showed that CB1 receptor activation by ACEA increased GABA release and caused a significant increase in food intake compared to animals receiving the vehicle, AM 251, or AM 251 + ACEA. In addition, this effect persisted for a period of 2 h. Finally, animals injected with AM 251 and AM 251 + ACEA exhibited food intake comparable to the vehicle condition. In summary, these findings suggest that increased food intake is primarily associated with GABAergic hyperfunction in the PVN rather than with hypofunction.

Corwin et al.[14] found a decrease in the gene expression of $GABA_B$ and $GABA_A$ receptors in rats with binge eating compared to the control group. Furthermore, the administration of GABAergic agonists in the dorsomedial and ventromedial regions of the PFC increased the binge size in the INT condition, without affecting the intake in the D condition.

In the study by Sato et al.[44], it was found that a 5% GABA intake significantly suppressed food intake and body weight gain compared to the other conditions, which did not show significant differences among themselves. In addition, this suppression was associated with significantly elevated concentrations of GABA in plasma.

The reduction in food intake could be modulated by alterations in taste, so that ingesting 5% GABA could have an unpleasant taste compared to 0.5% or 2%. To corroborate this hypothesis, vigabatrin was injected into

Table 2. Summary of the studies included in the systematic review on the GABAergic system and feeding behavior.

Brain region	GABAergic effect	Outcome on feeding behavior	References
Prefrontal cortex	↓ $GABA_B$ receptor expression	↑ Binge eating	14
Paraventricular nucleus	↑ GABA release (via cannabinoids)	↑ Hyperphagia	43
Lateral hypothalamus → Locus coeruleus pathway	↑ GABAergic activation	↑ Compulsive eating	41
Ventrolateral periaqueductal gray	↓ GABAergic activation	↑ Intake in food-deprived mice	40
Hippocampus	↑ GABA (vigabatrin)	↓ Food intake	44

mice exposed to these latter two conditions. The results indicate that the administration of vigabatrin significantly reduced GABA-T activity in the liver compared to the control groups. This resulted in an increase in circulating and cerebral (cortex and hippocampus) GABA levels, which, in turn, led to a decrease in food intake and body weight.

These findings rule out the explanation that the decrease in intake is due to the unpleasant taste of GABA in the diet. Instead, they suggest that the increase in GABA levels in the central nervous system may decrease food intake and body weight, in addition to its peripheral effects.

Discussion

The general objective of the study was to conduct a literature review on the functioning of the GABAergic system in binge eating episodes. Contradictory results were identified regarding the role of GABA in feeding behavior, as several studies reported variations in opposite directions. Some of these studies showed an increase in intake behaviors with either lower[14,40] or higher GABAergic activation,[41,43] while others reported the inverse relationship: reduced intake with either higher[40,44] or lower activation of the neurochemical circuit[41].

Variations in the protocol can lead to the application of procedures with different levels of sensitivity in detecting the phenomenon, which, in turn, could generate contradictory and ambiguous results. In this regard, it is interesting to note that studies conducted by Hao et al.[40] and Marino et al.[41] have yielded different results despite using similar techniques. This discrepancy could be attributed to differences in dependent variables and the duration of the trial used in their research.

Hao et al.[40] recorded both direct behaviors, referring to the amount of food consumed, and indirect behaviors, linked to the time spent on intake as well as the number of approaches to the food, over a period of 30 and 10 min, respectively, while Marino et al.[41] only observed indirect behaviors for one minute. Faced with this, it could be argued that an observation period of just one minute may be insufficient to adequately assess the impact of GABA on intake.

This discrepancy in the literature may be attributed not only to procedural differences but also to the specific neuroanatomical structures targeted (Table 2). The studies by Corwin et al.[14] and Cruz-Martínez et al.[43] reported opposing results following the administration of drugs that enhance GABA activity. These discrepancies could stem from differences in how the neurochemical pathways were manipulated. While Corwin et al.[14] directly administered GABAergic agonists into the PFC, Cruz-Martínez et al.[43] performed an indirect intervention using cannabinoid agonists targeting the PVN.

Role of the PFC in binge eating and GABAergic modulation

Regarding the PFC, a decrease in the gene expression of the $GABA_B$ receptor was found in binge-eating rats compared to the control group. Furthermore, the administration of GABAergic agonists in the dorsomedial and ventromedial regions of the PFC increased the binge size in the experimental condition, without affecting the intake in the control condition. Similarly, the administration of a dopaminergic antagonist of D_2-like receptors (i.e., SKF 81297) in the dorsomedial region produced effects similar to inhibition by GABA agonists[14].

These findings suggest that D_2-like receptors in the PFC are a key component in restraining binge-eating behavior. Binge-eating episodes may generate differential activation patterns within VTA neurons, potentially resulting in increased dopamine release in the PFC[14]. D_2-like receptors located on presynaptic neurons in this cortex would have an inhibitory effect on GABA release in the synaptic cleft. This would increase PFC activity and reduce binge-eating behavior[45].

The study by Corwin et al.[14] suggests binge-eating episodes serve to restore a hypofunctional reward circuit. For example, rats with binge-eating episodes show alterations in mRNA expression for tyrosine hydroxylase, the dopamine transporter, and the D_2-like receptor in the VTA. While binge-eating episodes normalize general aspects of dopaminergic signaling, they do not seem to have the same effect on mRNA expression of the D_1-like receptor and the $GABA_A$ receptor. There are also no normalizations in mRNA for tyrosine hydroxylase and the $GABA_B$ receptor in the PFC. The absence of these normalizations could lead to neuronal adaptations that perpetuate the dysfunctional eating pattern.

These findings suggest that initially, binge-eating episodes would lead to an increase in dopaminergic activity, and if this behavior persists over time, it would result in a subsequent desensitization of this reward system, reducing its activity, causing a hypofunction of the system. GABAergic activity would then be aimed at regulating dopaminergic activity, and this would help explain the differential effect of GABAergic agonists on rats with and without binge-eating episodes[14].

In summary, the PFC plays a crucial role in inhibiting binge-eating behavior. When GABA agonists are applied in this region in rats without a previous history of binge-eating episodes (group D), no hyperphagic effects are observed compared to a group that received a saline solution. This effect is only present in the condition with a previous history of binge-eating episodes (group INT), which has been associated with a decrease in GABAergic system function[14]. Conversely, the administration of Cannabinoid agonists that increase GABA release in the PVN induces hyperphagia in rats without a previous history of binge-eating episodes[43]. This could be because the PVN may play a central role in regulating satiety. It has been observed in previous studies that lesions in this structure can lead to hyperphagia[46]. Following this line of reasoning, it could be inferred that increased availability of GABA could inhibit the PVN, resulting in a decrease in the sensation of satiety and, consequently, exacerbating consumption.

Involvement of the PVN and hypothalamus

The modulation of feeding behavior by the hypothalamus exhibits variability depending on various factors, including the hypothalamic region involved in the process, as well as the afferent and efferent signals that this neural structure receives and sends to other anatomical structures. Previous literature suggests that a subset of GABAergic neurons in the LH project to the VTA, inhibiting its activity and promoting dopamine release. Consequently, activation of this GABAergic pathway would have a disinhibitory effect on VTA dopaminergic activity, meaning that LH stimulation can induce compulsive feeding by disinhibiting dopamine neurons[47]. While these data suggested that GABAergic cells in the VTA played a central role in feeding regulation, the study by Marino et al.[41] provided clarifying insights into this relationship. Overeating would be generated by GABAergic projections originating in the LH and terminating in the LC. Peripheral GABAergic neurons in the LC are a critical step in the descending circuit for LH neurons, whereas GABA neurons in the VTA are not. Activation of this pathway would be necessary and sufficient to induce overeating in satiated mice.

Functions of the vlPAG and associated circuits

The study by Hao et al.[40] also assigns an important role to the hypothalamus in feeding regulation. The authors found an increase in food intake and body weight on activation of $GABA_A$ receptors and on photoinhibition of GABAergic neurons in the anterior vlPAG. In addition, this region is activated by rostral projections to the BNST and connections to the LH. Stimulation of both pathways separately is necessary to induce overeating in food-deprived mice.

Hippocampal GABAergic influence on feeding behavior

Finally, hippocampal GABAergic pathways could play a role in regulating feeding behavior. In the studies by Sato et al.[44], a suppression of food intake was found with increased GABA availability. The authors propose three hypotheses regarding the suppressive effects of 5% GABA intake on feeding behavior: alterations in food taste, peripheral effects, and effects on the central nervous system. To test these hypotheses, daily doses of vigabatrin were administered alongside GABA diets that did not show a suppressive effect on intake (0.5% and 2%), resulting in reduced consumption compared to controls. The authors suggest that these data refute the explanation of alterations in taste.

On the other hand, vigabatrin is an inhibitor of the enzyme responsible for degrading GABA (GABA-T), leading to an increase in its availability. The study reported an elevation of GABA levels peripherally, in the cerebral cortex, and the hippocampus[44]. The authors

suggest that the suppression of intake could be explained by effects on the central nervous system: the increased neurotransmitter levels in the hippocampus and cerebral cortex. In addition to its widely reported actions on the hypothalamus[47], GABA regulates food intake and body weight by acting on the PFC and the hippocampus, where lower GABA levels are associated with greater body weight gain in rats fed a high-fat diet[48].

Limitations and future directions

Finally, certain limitations of this systematic review should be acknowledged. Although the studies included explored the role of the GABAergic system in feeding behavior, only one specifically employed an experimental model of binge eating to investigate BED. This limits the generalizability of the findings to the disorder. Consequently, further empirical research using validated BED models is necessary to clarify the involvement of GABAergic mechanisms and their interaction with the dopaminergic system during episodes of compulsive overeating.

In addition, the RoB assessment revealed some methodological weaknesses across the included studies, particularly related to the lack of blinding during intervention administration and unclear allocation concealment. These limitations, common in preclinical research, may have introduced performance and selection biases, underscoring the need for cautious interpretation of the results and for improved rigor in future animal studies on this topic.

Conclusion

In general, the literature suggests that low levels of GABA in the central nervous system are associated with overeating and obesity[49]. However, this neurotransmitter operates in various regions of the nervous system, and the underlying mechanisms mediating its influence on feeding behavior are highly complex and have not yet been fully elucidated. While the reviewed studies suggest that GABAergic activity is closely linked to feeding behavior, this relationship may vary depending on the specific neuroanatomical structure in which GABA is present and its connections with other regions of the central nervous system. Specifically, in the anterior vlPAG, it has been observed that suppressing the activity of GABAergic cells promotes feeding in satiated mice, while activating these cells inhibits food intake in food-deprived mice[40]. On the other hand, a connection has been established between lower GABA activity in the PFC and VTA and increased food consumption, especially in individuals with a history of binge eating episodes[14]. Conversely, in the hypothalamus, higher GABAergic activity in the PVN[43] or LH[41] is associated with increased intake. Finally, higher levels of GABA in the hippocampus and cerebral cortex are linked to reduced intake[44].

Indeed, these findings highlight the complexity of the mechanisms regulating feeding behavior, suggesting that it largely depends on the inactivation or activation of specific neuroanatomical regions linked to specific feeding functions.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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