Habenular nuclei linked with compulsion in alcoholism and obesity

Núcleos habenulares estão relacionados com compulsão no alcoolismo e obesidade

DOI:10.34117/bjdv8n5-298

Recebimento dos originais: 21/03/2022
Aceitação para publicação: 29/04/2022

João Victor Amaro de Souza
Acadêmico do Curso de Medicina
Instituição: Centro Universitário de Maringá - UNICESUMAR. PIC UniCesumar.
Endereço: Av. Guedner, 1610
E-mail: joaovamaros@gmail.com

Yasmin Catelan Mainardes
Acadêmica do Curso de Medicina
Instituição: Centro Universitário de Maringá - UNICESUMAR. PIC UniCesumar
Endereço: Av. Guedner, 1610
E-mail: yasmin.c_m@hotmail.com

Sandra Cristina Catelan - Mainardes
Orientadora, Mestre, Docente na área da Saúde da Unicesumar
Instituição: Unicesumar
Endereço: Av. Guedner, 1610
E-mail: sandra.mainardes@unicesumar.edu.br

ABSTRACT

Alcoholism, also known as "alcohol dependence syndrome", is a disease that develops after repeated use of alcohol, typically associated with binge eating. Obesity is the result of a combination of genetic and environmental factors. Compulsive eating is not caused by hunger or pleasure, but as a defense mechanism that prevents feelings of loneliness, failure and abandonment. The aim of the present research, of bibliographic nature, will be to discuss the relation of the habenula with the mechanism of compulsion for the consumption of alcohol and food. As a methodology, searches will be carried out in databases, in the last 10 years, in Pubmed. The descriptors "habenula", "obesity", "alcoholism" and "compulsion" will be used in articles written in English, French and Spanish. Seeking to relate the neural pathways of the habenula, with disorders triggered by excessive alcohol consumption and eating disorders, concerning the anatomical and functional aspects and the pathways of dependence. To this end, the authors propose to understand this relationship from a neurological perspective, with an emphasis on mental health, encompassing a neurobiological and social view. It is expected, with this research, to collaborate with the development of a new alternative regarding the treatment of these diseases, considering the habenula as a reference. It is hoped, with this research, to collaborate with the development of a new alternative regarding the treatment of the complication, considering the habenula as a reference, in order to promote an improvement in the quality of life and health promotion of these patients. It is hoped, with this research, to collaborate with the development of a new alternative regarding the

treatment of the complication, considering the habenula as a reference, in order to promote an improvement in the quality of life and health promotion of these patients.

Keywords: alcoholism, obesity, habenula, compulsion.

RESUMO

O alcoolismo, também conhecido como "síndrome da dependência do álcool", é uma doença que se desenvolve após o uso repetido de álcool, tipicamente associado a compulsão. A obesidade é o resultado da combinação de fatores genéticos e ambientais. O comer compulsivo não é provocado por fome ou prazer, mas como um mecanismo de defesa que evita sentimentos de solidão, fracasso e abandono. O objetivo da presente pesquisa, de cunho bibliográfico, será discutir a relação da habênula com o mecanismo de compulsão pelo consumo de álcool e alimentos. Como metodologia serão feitas buscas em bases de dados, nos últimos 10 anos, na Pubmed. Serão usados os descritores “habênula”, “obesidade”, “alcoolismo” e “compulsão” em artigos escritos em inglês, francês e espanhol. Buscando relacionar da estrutura neurológica, as vias neurais da habênula, com transtornos desencadeados pelo consumo excessivo do álcool e os transtornos alimentares, preocupando-se com aspectos anatomofuncionais e as vias de dependência. Para tanto, os autores se propõem a compreender esta relação a partir de um olhar neurológico, com aporte na área da saúde mental, englobando uma visão neurobiológica e social. Espera-se, com esta pesquisa, colaborar com o desenvolvimento uma nova alternativa quanto ao tratamento da compulsão, considerando a habênula como referencial, a fim de promover uma melhora na qualidade de vida e promoção da saúde destes doentes.

Palavras-chave: alcoolismo, obesidade, habênula, compulsão.

1 INTRODUCTION

The abuse of alcohol is a public health problem recognized for its direct influences, such as the number of hospitalizations for drug addiction, and indirect, such as expenses with secondary diseases and even complications of the same as traffic accidents; Just as obesity is, generating huge costs for the health system. (1-3)

According to the Survey of Risk Factors and Protection for Chronic Diseases by Telephone Survey, released by the Brazilian Ministry of Health, the obesity rate in the country went from 11.8% to 19.8% between 2006 and 2018. (4) Being slightly higher among women (20.7%) than among men (18.7%). Moura emphasizes that the extraordinary increase in these data justifies the importance of studying this disease as a determining factor in Brazilian public health. Alcoholic drink also worries. The frequency of alcohol abuse was 17.9%, being higher in men (26.0%) than in women (11.0%). (5)

As these are diseases with several triggering factors, studies of the triggering mechanisms and pathways are essential for the discovery of new ways to identify, prevent and treat them in advance. Machado points out that both share a very strong factor for

their consolidation in individuals: compulsion. (6) This factor is related to activation of areas of the limbic system, which is linked to emotions, such as the nucleus accumbens (NAc). However, there is another very important area, known to be inversely related to that of NAc, that has been related to these diseases: the habenula.

Located in the epithalamus, inferolaterally to the pineal gland, the habenula is composed of two nuclei: one lateral and one medial. The lateral nucleus receives afferences from the septal nuclei through the medullary stria of the thalamus and its efferences to the interpeduncular nucleus of the midbrain through the habenulo-interpeduncular tract; for the mesolimbic system, inhibiting dopaminergic neurons; and the raphe nuclei, inhibiting serotonergic neurons. For such relationships, the habituation is being closely related to mood disorders such as depression. (7)

Because it has a mechanism of inhibition rather than a reward system like NAc, habenula may be related to the mechanism of consolidation of alcohol addiction and binge eating obesity. (8, 9)

Thus, the close relationship of these factors together with the extraordinary increase in public spending (direct and indirect), justifies the importance of knowing these diseases and looking for the best method to treat them. Being an innovative method that guarantees new perspectives for the treatment of these diseases, the investigation of the relationship between habenula and these processes guarantees a promising future as the reduction of such alarming rates. (1-3)

Therefore, the objective of this study is to evaluate, based on the literature, the relationship between habenula and alcoholism and obesity, by verifying studies related to this theme.

2 MATERIALS AND METHODS

2.1 SEARCH STRATEGY

The authors conducted from May 10th to October 31st, 2019 an integrative review concerning the pathophysiological associations of the habenula with alcoholism and obesity on the PubMed. The keywords used was the association of “habenula” AND “alcohol” OR “compuls*” OR “obesity” and full text were used as filters.

2.2 STUDY SELECTION

After the duplicates were removed, the articles were screened analyzing the following criteria: full article availability; and in English, Portuguese or Spanish. Then,

the authors screened the articles in order to select only the ones that fitted the proposed objective. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow chart summing the articles selection is exposed below at Figure 1 and the articles included are demonstrated at Table 1. (10, 11)

The search strategy resulted in 57 articles on the PubMed database, from which 2 were duplicates and, so, removed, leaving 55 papers. One of those papers was removed because it did not meet the full text availability and language criteria. Of the last 54 articles, 24 were excluded because they addressed different themes from the proposal presented as the objective of our work. Leaving, at last 30 papers that were included in our discussion.

3 DISCUSSION

3.1 ALCOHOLISM

Of the thirty articles analyzed, 27 of them (90%) linked habenula to alcohol or obesity. When articles related to alcohol were examined, it was shown that the most frequent mechanism demonstrated was mediated by the glutamatergic influence. clarifies that the habenula is divided into two nuclei: lateral (LHb) and medial (MHb), the former depolarizing when exposed to an aversive situation.

A study by Li, Kang, et al. inhibited the AMPA glutamatergic receptor and CAMKII activity (both acting on Glu A1 phosphorylation) in rats with ethanol-induced behavior in abstinence, showing that it decreases neuronal activities, decreasing alcohol intake and symptoms depression-like. (12)

Fu et al. analyzed using immunohistochemistry and anatomical tracking of the LHb circuit with low-dose ethanol. The ethanol solution was injected into the peritoneum of the mice, where they found an increase in neurons immunoreactive to cFos in LHb. Most of them expressed a marker of the glutamatergic phenotype, the vesicular glutamate transporter 2 (vGluT2). These neurons emitted efferent pathways to the ventral tegmental area, the rostromedial tegmental nucleus and the dorsal raphe. Then, using the antegrade tracer AAV-CaMKIIa-eGFP in the lateral hypothalamus, the authors found that LHb, under the influence of ethanol, received pathways from this area. (13)

Stevenson et al. (2019) studied the relationship between metabotropic glutamate type 5 receptor activity (mGluR5) and locomotor sensitization induced by ethanol in mice. The authors divided the rats into two groups, one using an MPEP (negative allosteric modulator) from MGluR5 before ethanol consumption and the other without

previous MPEP. After 9 days of induction, the authors tested the locomotor response to ethanol and found that rats that did not receive MPEP had an increase in kinase immunoreactivity regulated by extracellular signal (ERK1 / 2) in the accumbens nucleus shell and a decrease in LHb. In addition, after the induction period, the authors found a significantly different locomotor response within and between groups. Kang et al. (2018) showed that the expression of the glutamatergic protein GLT-1 was reduced in the LHb of abstinent rats. (14, 15)

The work of Kononoff et al. (2018) shows that, using a systemic administration of the GPR139 agonist, JNJ-63533054, in alcohol-dependent rats, reversed the escalation of self-alcohol intake and decreased the hyperalgesia induced by the withdrawal syndrome, but did not decrease its somatic signs. In addition, when injected directly into the medial habenula (MHb), the authors found that the drug reduced withdrawal-induced hyperalgesia and self-administration of alcohol in dependent rats. However, JNJ-63533054 was effective only in rats with compulsive alcohol intake. (16)

In addition to the direct influence of glutamate, the work of Gregor et al. (2019) demonstrated that the TRPV1 intra-habenular antagonist administered to rats with alcohol withdrawal led to a reduction in hyperalgesia, behavior similar to anxiety and, once alcohol consumption was resumed, showing that TRPV1, mediated by glutamatergic pathways, can contribute to the aberrant behaviors observed in alcohol withdrawal. (17)

Another neurotransmitter that showed a strong influence on the mechanism of alcohol dependence was dopamine. The article by Zuo, Fu, et al. (2017) states that, mediated by dopamine D1 receptor (D1Rs) via cAMP that increase LHb glutamatergic signaling, the conditioned aversive effects of alcohol intake are related. The study by Glover et al. (2016) showed that the lateral habenula, via activation of the rostromedial tegmental nucleus and, the last inhibitor of the dopaminergic pathway, plays an important role in the aversion properties of alcohol in rats. In their analysis, Alba-Ferrara et al. (2014) stated that the lateral habenula is a possible target for deep brain stimulation in the treatment of chronic alcoholism due to its GABAergic control of the dopamine reward pathway in the midbrain. He also pointed out that the animal models that tested this theory had good results and need to be transposed to tests on humans using functional magnetic resonance imaging or high-resolution magnetic resonance imaging and manual screening of LHb limits with stereotactic atlas in T1. LHb receives connections from the medial prefrontal cortex, nucleus accumbens, caudate and putamen and emits connections with the ventral tegmental area and the substantia nigra. The authors point out a relationship

between the susceptibility of habenular neurons to the toxicity of manganese and the fact that manganese is the only element that accumulates in alcoholic brains. Adding this to the fact that the deposition of manganese emits a contrast of T1w MRI, they suggest that it can be used to achieve LHb by image in order to position the deep brain stimulator (DBS) correctly. (18-20)

Type M potassium channels have also been shown to be part of the mechanism that regulates the influence of habenula on chronic alcohol. The study by Kang et al. (2019) showed that rats with induced alcoholism had a negative regulation of the type M potassium channel that led to hyperalgesia when these animals were placed in a state of abstinence. Kang et al. (2017) showed that rats with symptoms of ethanol withdrawal had a higher baseline trigger rate and excitability in LHb neurons, but a lower M + K current and mean post-hyperpolarization range when compared to rats without ethanol. In addition, the protein expression of the KCNQ2 / 3 M channel subunits in the increase induced by LHb and M channel blockers (XE991) in these regions was lower in the ethanol withdrawal neurons than in the naïves. (21, 22)

In a review, Shah et al. (2017) explained that LHb has afferent neurons coming from: medial prefrontal cortex (through the medullary streak), pale globe, dopaminergic ventral tegmental area (ATV), dorsal raphe nuclei, lateral hypothalamus (glutamatergic); and efferent neurons going to ATV, substance nigra pars compacta (SNc) dorsal and median raphe nuclei (5-HT), rostromedial mesopontine tegmental nucleus (GABA) and periaqueductal ash (enkephalin). The authors stated that LHb neurons are activated by acute intake of alcohol in low doses, are hyperactive during withdrawal syndrome and are less sensitive to acute alcohol during withdrawal from chronic consumption. The article also points out that, in acute situations of alcohol ingestion, the transmission of glutamate in LHb is increased and is related to behavioral changes in alcohol intake. Finally, they show that, through negative regulation of M-type potassium channels, the intrinsic excitability of LHb neurons is increased in abstinent rats, as well as the symptoms of anxiety in them. (23)

The study by Li et al. (2019) showed that intra-LHb glycine rescues anxiety and depression in rats with alcohol withdrawal and reduces alcohol intake after access. On the other hand, intra-LHb strychnine induces these symptoms in naïve rats. GlyRs have been shown to be blocked by strychnine. The frequency and amplitude of spontaneous post-synaptic inhibitory current (IPSCs) were lower in abstinent rats. The perfusion in a depolarizing internal current bath induced by strychnine and the increased action potential

trigger LHb neurons. All these data point to a tonic inhibition of glycine in the physiological and pathological conditions of LHb neurons. The authors also showed that activating GlyRs reverses LHb hyperactivity, reduces alcohol intake and alleviates aberrant behavior. (24)

In the only study that used pregnant mice, Cantacorps et al. (2018) analyzed the influence of contact with alcohol on pregnancy and lactation on metabolism and neural connections in adults. The authors showed that the mice with pre- and post-natal exposure to alcohol showed a reduction in the activity of cytochrome C oxidase (CCO) in the LHb of these mice, which was congruent with the attenuation of the alcohol-induced reward effects observed in them. (25)

Two studies have shown the influence of nicotine receptors (nAChR) on ethanol withdrawal syndrome. The review by Mclaughlin et al. (2017) showed that blocking nAChR in the nucleus circuit of the medial - interpeduncular habenula can cause ethanol withdrawal syndrome and that the absence of neuropeptide Y mRNA in rats increases alcohol intake. In their study, Perez et al. (2015) subjected a group of rats to an intrahabenular microinjection (MHb) and inside the interpeduncular nucleus of a non-selective nicotine receptor antagonist, mecamylamine, which led to a precipitation of the physical signs of ethanol withdrawal. (26, 27)

Only Li, Fu, et al. (2017) showed the effects of electroacupuncture (AE) attenuation on hyperalgesia induced by ethanol withdrawal and its relationship with the lateral habenula. The rats submitted to AS showed results that suggest a decrease in hyperalgesia caused by the withdrawal syndrome. In addition, a subgroup of animals had a cannula implanted inside their habenulas and, in part, a mu opioid receptor (MOR) antagonist, naltrexone, was injected into the cannula prior to EA therapy. The authors found that mice with naltrexone exhibited more painful behavior than those without, leading to the conclusion that MOR in LHb plays an important role in hyperalgesia caused by ethanol withdrawal. (28)

Li et al. (2016) in his article, showed that rats with ethanol withdrawal showed expression of the c-Fos protein, spontaneous action potential trigger and spontaneous excitatory postsynaptic currents, all increased when compared to ethanol naïves. It also showed that, although low-frequency stimulation does not diminish these changes, high-frequency stimulation does so, being a possible target for the treatment of alcoholism. (29)

The only article addressing the serotonergic (5-HT) role, Zuo et al. (2019) studied the 5-HT2Rs and CaMKII signaling pathway in the habenula and its adaptation and nociceptive sensitivity in rats with alcohol withdrawal symptoms. The authors showed that this pathway induced hyperglutamatergic transmission and LHb hyperactivity, as well as nociceptive sensitivity in rats removed from ethanol and acute ethanol intake in LHb neurons. Given these mechanisms, they suggest that serotonergic signaling in the lateral habenula may be a therapeutic target for alcohol dependence and associated aversive behaviors. (30)

While previous works presented receptors or neurotransmitter pathways that show the influence of alcohol on the physiology of the habenula, one of the analyzed articles described a different point of view. Roux et al. (2015) demonstrated the increase of a neuroinflammation-inducing lipid, ceramide, in LHb in rats with chronic ethanol consumption. (31)

Finally, there were two studies that used direct injuries to the habenula to perceive changes in behavior between groups. Tandon et al. (2017) registered neural firing in the free-acting LHb before and after aversion to conditioned flavor (CTA) induced by ethanol to the taste of saccharin. The authors described four main differences between the shots before and after the CTA: 1) the initial shot after the CTA was significantly greater; 2) triggering evoked by cues using the availability of saccharin as altered signals from mainly inhibition (bCTA) to mainly excitation (aCTA); 3) the lever evoked inhibition showed a decrease in its aCTA magnitude; 4) the burning rates were significantly higher during the devalued consumption of the aCTA saccharin solution. Finally, the rats underwent surgery to implant an electrode in the LHb and were divided into two groups: electrode with current (LHb lesion) and electrode without current (simulated lesion). When the authors compared the two groups, they found that the LHb lesion significantly attenuated the effects of CTA. The experiment by Sheth et al. (2017) demonstrated that, by damaging the LHb afferent pathway of the lateral hypothalamus by the medullary streak (SM), the voluntary ethanol intake in the studied rats increased. However, the projection of the ventral pale did not show significant changes in the voluntary consumption of ethanol operating on self-administration of ethanol, extinction of self-administration of ethanol or reinstatement induced by yohimbine. But it is prudent to consider injuries from adjacent regions. (32, 33)

Although most studies have demonstrated this link, three articles have found no relationship between habenula itself and alcohol. One of the studies described that, with

the reestablishment induced by the "cue" of the alcohol-seeking behavior, the piriform cortex, NAc, amygdala, lateral septum and mediodorsal thalamus showed an increase in CaMKII phosphorylation, while the same change was not observed in the habenula in those rats. (Salling et al., 2017). In their study, Donaire et al. (2019) stated that the group submitted to LHb showed no changes in ethanol consumption. The other showed that histaminergic neurons in the posterior hypothalamus tuberomamilar nucleus showed an increase in nicotine α7 receptors in rats with a preference for alcohol versus alcohol-avoiding rats, but when they analyzed nicotine α6 receptors in the medial habit, there was no difference between groups. (Nuutinen et al., 2016) (34-36)

4 OBESITY

Binge eating is closely related to the limbic system and its reward system through brain pathways. Studies published in recent articles have shown a new protagonist to this whole system: habenula. A collection of articles brought up the relationship of this area with several areas of the brain and their participation in obesity. The first studies used the dopaminergic pathway and its relationship with the brown adipose tissue thermogenesis as a precursor of this problem.

A study by Ootsuka e Mohammed (2015), Ootsuka *et al (* 2017) e Brizuela *et al (* 2019) shows the relationship between lateral habenula (LHb) with medullary rafe core, from experiments with mouse. Point of that, the principal via of regulation is LHb, that when activated regulates the thermogenesis of brown adipose tissue which, envolves the neural pathway to sympathetic control center of lower brain stem at Rafe's core, works like as integrating center of lower brain stem through direct stimuli to sympathetic neurons of vertebral column.

By the fact LHb and rafe core do not connect, this modulation occurs indirectly by ventral tegmental area (ATV). This area contains neurons synthesizers of dopamina that are inhibited by GABA neurons stimulated in the tail of the ATV, more precisely in tegmental nucleus of the rostromedial mesopontine. (OOTSUKA e MOHAMMED, 2015; OOTSUKA *et al.*, 2017; BRIZUELA *et al.*, 2019).

Ootsuka (2015) e Brizuela et al (2019) evaluated the termogenesis efect induced by LHb at ATV. For that they performed experiments on Sprague – Dawley male mouse, with procedures approved by the Animal Welfare Committee of the University of Flinders. The procedure was performed through electrical discharges and injection of specific drugs for stimulation of neurons. In order to relate with ATV, added muscimol

(receptor agonist of GABA), and it was observed increase thermogenesis consequently the body temperature. To relate LHb via, used bicuculin injections (GABA receptor antagonist), and the results showed an increase in thermogenesis. Thus, it was perceived that the excitatory thermogenic effect of LHb stimulation is mediated by an inhibitory link to ATV, inferring that ATV could be part of the neural circuit that connects the LHb in the medullar Rafe. Thus, they concluded that dopamine have a fundamental role in the sympathetic inhibition of brown adipose tissue and, therefore, in the decrease of thermogenesis, consequently increasing body weight. (OOTSUKA e MOHAMMED, 2015; BRIZUELA et al., 2019).

Ootsuka et al (2017) proposed to prove the relationship between the lateral habenula and thermogenesis. He used LHb as the methodology for the lesion of the area in question. The authors resulted in a decrease in body temperature, suggesting that this structure is part of the emotional hyperthermia circuit.

Other neurotransmitters may be envolved with this mechanism. By Stamatakis et al (2016) some glutamategic neurons of the lateral hypothalamic area (LHA) that are projected by lateral habenula (LHb), generating behavioral evasion by inhibition of dopaminergic neurons of the ventral tegmental area. It is important to highlight that LHA is an area that contains GABA-type neurons and glutamategists, which produce distinct behavioral phenotypes. So to prove the relationship between obesity and these brain areas, Stamatakis *et al.* (2016) performed a procedure that counted in a first moment, with the genetic ablation of the glutamategic neurons of the LHA by the injection of a virus. It was observed that after this procedure, the mouses had a predilection for fat food and for a heat-dense and palatable liquid, generating a considerable weight gain.

This is because, when removing the glutamate neurons, there is a prevalence of GABAergics to perform eferences to LHb. And this relationship between LHA and LHb was proven from the mapping of the circuit from a cremation-induced viral construct, in which it was noted from the release of optical pulses in the cells of LHA an increase in the rate of firing of neurotransmitters in the post synaptic of LHb neurons, proving the connectivity of both. This study allowed the authors to conclude that there is a relationship between the hypothalamic lateral area and the lateral habenula. This relationship modulates the reward process related to weight gain and consequently obesity. Finally, these authors make it clear that this connectivity is dynamic and can be monitored for stress or other environmental factors.

Among the selected articles where the descriptors: habenula and obesity were found, some of them did not establish a relationship between the reward system and the habenula as well as its modification when stimulated. The article by Blancas-Velasquez et al (2018) considered the modulation of the expression of the biological clock genes per2, Clock and Bmal1 to relate obesity.

Blancas- Velasquez et al (2018), conducted a study with male Wistar night mouse, found that by adding a low diet fat free and high sugar (fcHFHS) for six months and comparing it with normal mouses, a considerable weight gain was observed at the first. Regarding genes, he interrupted the day-night differences in the Per2 expression of mRNA in the accumbens nucleus (NAc) and in the lateral hypothalamus, but not in the suprachiasmatic nucleus, the habenula and the ventral tegmental area.

The same author explains that night mouses usually have a highest of food consumption standard at night when compared to day, this is because light is the main via of alteration of clock genes involved in the transcription of proteins related to the circadian rhythm. This rhythm is controlled by the suprachiasmatic nucleus (NSC) from the repression or action of the clock genes. The genes involved in this process are per2, Clock and Bmal1. Normally there is an increase in the expression of genes at night, but by adding a diet rich in sugar and poor in fat, we realize that this difference day-night was absent in NAc and the habenula only for the gene per 2.

Adding to this study, the article by Blancas -Velasquez et.al (2017) also makes an experiment with mouse about the high sugar and low in fat diet (fcHFHS) and analyzes the per 2 gene involved, it was found that it usually changes the diurnal food consumption pattern in most brain areas related to the reward system and daily rhythm of food consumption (such as LHB). It also confirmed the theory that this diet is a successful model for inducing calorie intake, body weight gain and fat tissue accumulation in mice. Finally, he added the way they added the food: the rats ingest a similar amount of sugar during the day (rest phase) and during the night (active phase), but keeps the rhythmic intake of common food, this phase of changing consumption pattern that alters the circadian rhythms in the brain.

Relating this process to the main area of our study: LHb, we could think that by the habenula making direct glutamategic projections for LHb this area would present the same pattern as that: there would be no significant changes day-night, but that is not what the study demonstrated.

A single study of those previously selected, proposed by Hultman et al (2019) related the receptors for the fibroblast growth factor (FGF) with the medial habenula (MHb). Being controlled by the beta klotho enzyme (klb) that activates FGF proteins that bind to FGFR receptors to regulate peripheral glucose homeostasis in obese patients, a variety of receptors isoforms present in many regions of the SNC can be observed. One of these varieties is the expression of FGFR4 which is located only in the medial habenula and in the subcommisural organ of mice. Thus, it is understood that this region has glucose sensitive neurons and regulates obesity. Finally, in relation to enzymes, they are present restrictedly in the suprachiasmatic nucleus (NSC), but in the hypothalamus, although it has little expression when performing the digital droplet PCR test (ddPCR) in mice, a genuine population was perceived in this area.

Faced with such discoveries, there is one doubt: would it be possible to intervene in these neural mechanisms? According to Dupré et al (2015) suggests that there is an alternative for the treatment of obesity using deep brain stimulation (DBS) as a method, since it causes oscillations in brain signaling, restoring synchronization between the various areas of the brain. The study analyzes several areas, and their relationship with. It was observed that, for example, the hypothalamus has long been known to govern homeostatic food control, and the ventral striated (VS) begins the unit or initial motivation to seek food. The dopaminergic pathways (DA) of the striated ventral are related to pleasure, reward and addiction. In obesity these pathways are unregulated. Thus, there is a concern of DA modulation, because it has been observed that in obese individuals, there is a fault in the dopamine D2 receptor. A decrease in this neurotransmitter generates a constant search for satiety, resulting in weight gain. As the hypothalamus is the main reward path, by altering this whole process, it also alters many nucleus involved in this system, such as ATV and NAc which ended up increasing the activity associated to wishes in response to nutrients such as lipids and sugars. The practice of DBS, in this case should neutralize the unit of pleasure in eating.

The author highlights that the lateral hypothalamic area (HLA) is the main target of DBS, since it is the center of all circuits involved in food compulsion. This domino effect area signals a cascade of reactions that affect the sites that it affects, especially the limbic system and the associative circuits involved in the hedonic and homeostatic aspects of food seeking behavior. This change involves an increase in the dopaminergic reward system that plays a role in food compulsion, which can improve willpower, decrease the pleasure boost, increase the metabolic rate, and improve or inhibit, as necessary, the

functionality of these knots and pathways that are altered in individuals with obesity. In addiction, by integrating the DA reward pathways (through the medullar striation of the thalamus) with cognitive processes and emotion, we arrive at the alteration of the lateral habenula, since it participates in the making of motivational or value based decisions, being part of this circuit.

The authors of this study suggest for the control of obesity a proposal to make available new constant current, directional current electrodes and closed circuit devices that activate aberrant signaling pathways when necessary, and add the importance of this method in the treatment of food compulsion, by expanding new perspectives related to this subject. (DUPRE et al., 2015)

Two other studies selected with the descriptors, it was noticed that the habenula can be related to other mechanisms besides obesity: the control of chronic pain and drug consumption.

One of them was proposed by Senba (2017), who related the lateral habenula (LHb) to chronic pain, being related to lack of physical exercise. The hypothalamic and reward system, mesolimbic dopaminergic system, besides being part of food intake, energy metabolism, also influences the practice of physical activity. Chronic pain (especially neuropathic pain) is related to lifestyle, and has an intimate relationship with body inactivity. In order to release dopamine it is necessary to activate the neurons of ATV afference. There are two main sources of ATV entry, one is the lateral habenular nucleus and the other is the pontinal tegmental nucleus.

The chronic pain activates the LHb neurons that contain glutamate, are projected to the gabaergic neurons in ATV that promote an inhibition of dopamine release. Thus LHb is related to chronic pain.

Finally, the other study related the medial habenula (MHb) to drug consumption. Proposed by Ramsay (2015), it was identified that the alpha 5 nicotinic subunit of acetylcholine receptor transcribed from a CHRNA5 gene harbors multiple polymorphisms that affect the expression of mRNA altering the coded subunit, increasing the risk of dependence on various drugs. In habenular tissues, the expression of this gene is high, which reduces nicotine consumption in rats suggesting that the expression of the receptor alpha 5 mediates the sign of negative reward via habenulo-interpenduncular.

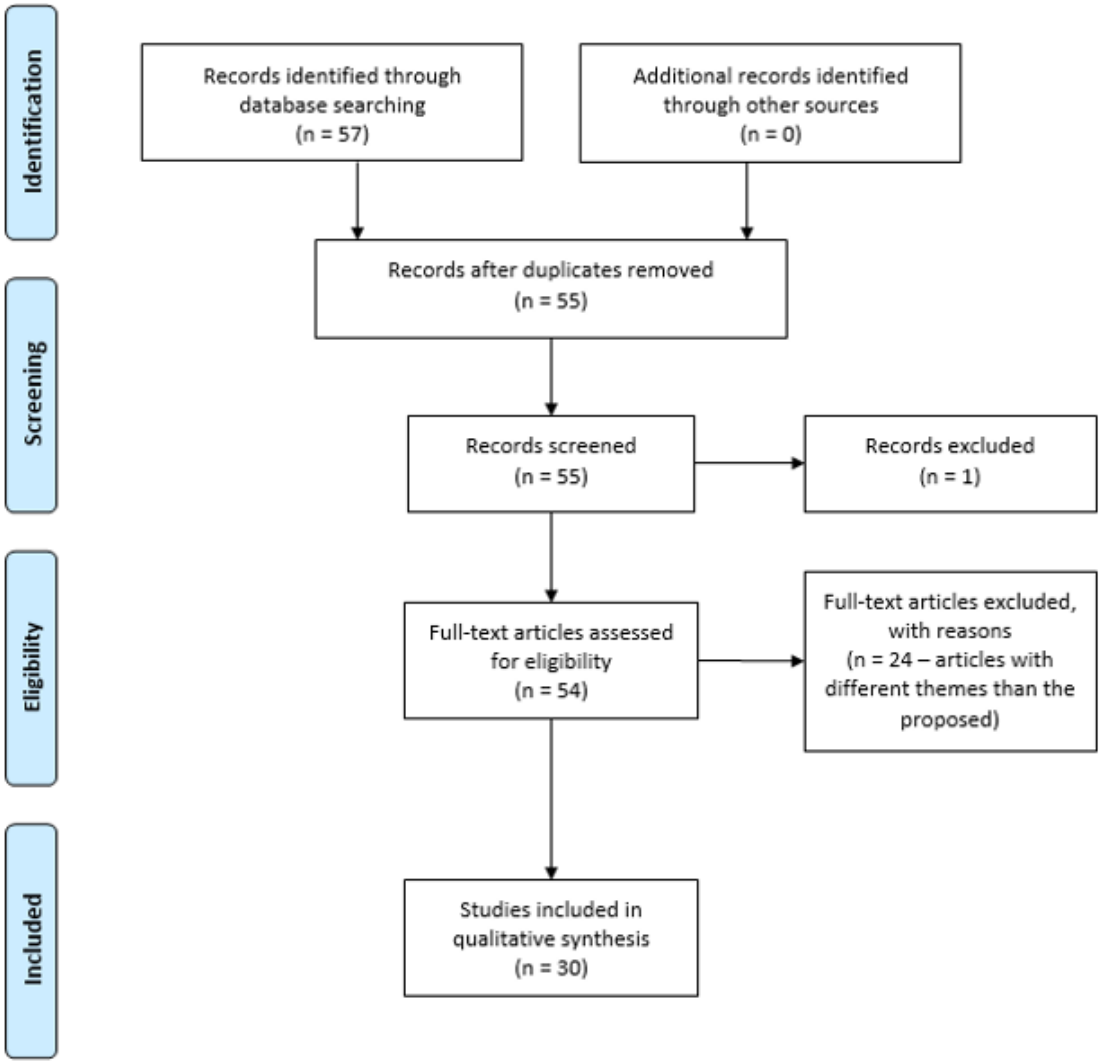
5 CONCLUSION

Although some studies show no link, 27 of the 30 articles analyzed demonstrated that the habenula, in any of its nuclei, plays an important role in the chronic physiology of alcohol intake, mainly in the withdrawal symptoms and conditioned taste aversion (CTA); or obesity. In both situations, the habenula is strongly related to the compulsive behavior associated with them. All of this endorses its role as a possible target for these conditions, whether to target drug delivery systems or neurosurgical procedures, such as ablation or neuromodulation by Deep Brain Stimulation. However, further studies on human models are needed to materialize this possibility.

The greater involvement of society with the use of medicines in the elderly, especially in polypharmacy, is due to the guidance to the elderly, in a careful and cautious way, about the care with their use, in order to promote an improvement in the quality of life. and promoting the health of the elderly. It is extremely important that this work serves as a contribution to a guiding experience for future research.

5.1 PRISMA

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow-chart showing the article's screening and selection(10).



REFERENCES

1. Galduróz JCF, Caetano R. Epidemiologia do uso de álcool no Brasil. Brazilian Journal of Psychiatry. 2004;26:3-6.

2. Arroyo-Johnson C, Mincey KD. Obesity Epidemiology Worldwide. Gastroenterol Clin North Am. 2016 Dec;45(4):571-9.

3. Smith KB, Smith MS. Obesity Statistics. Prim Care. 2016 Mar;43(1):121-35, ix.

4. <Vigitel.pdf>.

5. Moura EC, Malta DC. Consumo de bebidas alcoólicas na população adulta Brasileira: características sociodemográficas e tendência. Revista Brasileira de Epidemiologia. 2011;14:61-70.

6. <MACHADO - Neuroanatomia Funcional - 3ªed.pdf>.

7. <Ryan Splittgerber - Snell's Clinical Neuroanatomy (2018, LWW).pdf>.

8. Shah A, Zuo W, Kang S, Li J, Fu R, Zhang H, et al. The lateral habenula and alcohol: Role of glutamate and M-type potassium channels. Pharmacol Biochem Behav. 2017 Nov;162:94-102.

9. Zuo W, Wang L, Chen L, Krnjevic K, Fu R, Feng X, et al. Ethanol potentiates both GABAergic and glutamatergic signaling in the lateral habenula. Neuropharmacology. 2017 Feb;113(Pt A):178-87.

10. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009 Jul 21;6(7):e1000097.

11. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. meta-analysis protocols (PRISMA-P) 2015 : elaboration and explanation. 2015;7647(February 2011):1--25.

12. Li J, Kang S, Fu R, Wu L, Wu W, Liu H, et al. Inhibition of AMPA receptor and CaMKII activity in the lateral habenula reduces depressive-like behavior and alcohol intake in rats. Neuropharmacology. 2017;126:108-20.

13. Fu R, Mei Q, Zuo W, Li J, Gregor D, Bekker A, et al. Low-dose ethanol excites lateral habenula neurons projecting to VTA, RMTg, and raphe. Int J Physiol Pathophysiol Pharmacol. 2017;9(6):217-30.

14. Stevenson RA, Hoffman JL, Maldonado-Devincci AM, Faccidomo S, Hodge CW. MGluR5 activity is required for the induction of ethanol behavioral sensitization and associated changes in ERK MAP kinase phosphorylation in the nucleus accumbens shell and lateral habenula. Behav Brain Res. 2019 Jul 23;367:19-27.

15. Kang S, Li J, Bekker A, Ye J-H. Rescue of glutamate transport in the lateral habenula alleviates depression- and anxiety-like behaviors in ethanol-withdrawn rats. Neuropharmacology. 2018;129:47-56.

16. Kononoff J, Kallupi M, Kimbrough A, Conlisk D, de Guglielmo G, George O. Systemic and Intra-Habenular Activation of the Orphan G Protein-Coupled Receptor GPR139 Decreases Compulsive-Like Alcohol Drinking and Hyperalgesia in Alcohol-Dependent Rats. eNeuro. 2018 May-Jun;5(3).

17. Gregor DM, Zuo W, Fu R, Bekker A, Ye J-H. Elevation of Transient Receptor Potential Vanilloid 1 Function in the Lateral Habenula Mediates Aversive Behaviors in Alcohol-withdrawn Rats. Anesthesiology. 2019;130(4):592-608.

18. Zuo W, Fu R, Hopf FW, Xie G, Krnjević K, Li J, et al. Ethanol drives aversive conditioning through dopamine 1 receptor and glutamate receptor-mediated activation of lateral habenula neurons. Addiction biology. 2017;22(1):103-16.

19. Glover EJ, McDougle MJ, Siegel GS, Jhou TC, Chandler LJ. Role for the Rostromedial Tegmental Nucleus in Signaling the Aversive Properties of Alcohol. Alcohol Clin Exp Res. 2016 Aug;40(8):1651-61.

20. Alba-Ferrara L, Fernandez F, Salas R, de Erausquin GA. Transcranial Magnetic Stimulation and Deep Brain Stimulation in the treatment of alcohol dependence. Addict Disord Their Treat. 2014 Dec;13(4):159-69.

21. Kang S, Li J, Zuo W, Chen P, Gregor D, Fu R, et al. Downregulation of M-channels in lateral habenula mediates hyperalgesia during alcohol withdrawal in rats. Scientific reports. 2019;9(1):2714-.

22. Kang S, Li J, Zuo W, Fu R, Gregor D, Krnjevic K, et al. Ethanol Withdrawal Drives Anxiety-Related Behaviors by Reducing M-type Potassium Channel Activity in the Lateral Habenula. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2017;42(9):1813-24.

23. Shah A, Zuo W, Kang S, Li J, Fu R, Zhang H, et al. The lateral habenula and alcohol: Role of glutamate and M-type potassium channels. Pharmacology, biochemistry, and behavior. 2017;162:94-102.

24. Li W, Zuo W, Wu W, Zuo QK, Fu R, Wu L, et al. Activation of glycine receptors in the lateral habenula rescues anxiety- and depression-like behaviors associated with alcohol withdrawal and reduces alcohol intake in rats. Neuropharmacology. 2019;157:107688-.

25. Cantacorps L, Gonzalez-Pardo H, Arias JL, Valverde O, Conejo NM. Altered brain functional connectivity and behaviour in a mouse model of maternal alcohol binge-drinking. Prog Neuropsychopharmacol Biol Psychiatry. 2018 Jun 8;84(Pt A):237-49.

26. McLaughlin I, Dani JA, De Biasi M. The medial habenula and interpeduncular nucleus circuitry is critical in addiction, anxiety, and mood regulation. J Neurochem. 2017 Aug;142 Suppl 2:130-43.

27. Perez E, Quijano-Carde N, De Biasi M. Nicotinic Mechanisms Modulate Ethanol Withdrawal and Modify Time Course and Symptoms Severity of Simultaneous Withdrawal from Alcohol and Nicotine. Neuropsychopharmacology. 2015 Sep;40(10):2327-36.

28. Li J, Fu C, Liu H, Fu R, Zuo W, Kang S, et al. Electroacupuncture Attenuates Hyperalgesia in Rats Withdrawn from Chronic Alcohol Drinking via Habenular Mu Opioid Receptors. Alcohol clin exp res. 2017;41(3):637-43.

29. Li J, Zuo W, Fu R, Xie G, Kaur A, Bekker A, et al. High Frequency Electrical Stimulation of Lateral Habenula Reduces Voluntary Ethanol Consumption in Rats. Int J Neuropsychopharmacol. 2016 May 27.

30. Zuo W, Wu L, Mei Q, Zuo Q, Zhou Z, Fu R, et al. Adaptation in 5-HT(2) receptors-CaMKII signaling in lateral habenula underlies increased nociceptive-sensitivity in ethanol-withdrawn rats. Neuropharmacology. 2019;158:107747-.

31. Roux A, Muller L, Jackson SN, Baldwin K, Womack V, Pagiazitis JG, et al. Chronic ethanol consumption profoundly alters regional brain ceramide and sphingomyelin content in rodents. ACS Chem Neurosci. 2015 Feb 18;6(2):247-59.

32. Tandon S, Keefe KA, Taha SA. Excitation of lateral habenula neurons as a neural mechanism underlying ethanol-induced conditioned taste aversion. J Physiol. 2017 Feb 15;595(4):1393-412.

33. Sheth C, Furlong TM, Keefe KA, Taha SA. The lateral hypothalamus to lateral habenula projection, but not the ventral pallidum to lateral habenula projection, regulates voluntary ethanol consumption. Behav Brain Res. 2017 Jun 15;328:195-208.

34. Salling MC, Hodge CJ, Psilos KE, Eastman VR, Faccidomo SP, Hodge CW. Cue-induced reinstatement of alcohol-seeking behavior is associated with increased CaMKII T286 phosphorylation in the reward pathway of mice. Pharmacol Biochem Behav. 2017 Dec;163:20-9.

35. Donaire R, Moron I, Blanco S, Villatoro A, Gamiz F, Papini MR, et al. Lateral habenula lesions disrupt appetitive extinction, but do not affect voluntary alcohol consumption. Neurosci Lett. 2019 Jun 11;703:184-90.

36. Nuutinen S, Panula P, Salminen O. Different Hypothalamic Nicotinic α7 Receptor Expression and Response to Low Nicotine Dose in Alcohol-Preferring and Alcohol-Avoiding Rats. Alcohol clin exp res. 2016;40(2):329-34.