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Amygdala and Taste Learning

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1. Introduction

The amygdala is a particular forebrain structure which is widely involved in many cognitive processes, such as attention and emotional learning, among others. The amygdala is part of the limbic system, which is critical for survival. In rats, it is located bilaterally in the medial temporal lobes, and its nuclei are similar to those of primates [1, 2]. In mammals, the amygdala is involved in the expression of many behaviours, such as fear responses, reproduction, aggressiveness and social behaviour and also in physiological processes such as modulation of the neuroendocrine and autonomic systems and homeostasis [3]. The amygdala consists of several nuclei that form a complex network of information processing. The three main nuclei of this structure are the medial, the central and the basolateral nucleus. These nuclei have complex connections with other structures; therefore it is thought that the activity of the amygdala is relevant in the modulation of some types of learning and memory [4]. In particular, the amygdala appears to participate in several complex processes underlying taste learning [5-11].

This chapter will summarize the most relevant data from animal models involving the amygdala in three complex processes underlying associative learning using a taste stimulus. The first section will aim to describe the role of the amygdala in the acquisition of the conditioned taste aversion (CTA) learning, a particular conditioning in which the subject learns to associate a novel taste stimulus with a successive visceral discomfort. The second section will review the data evidencing the role of the amygdala in the latent inhibition process of CTA that is obtained when the taste stimulus is presented to the subject several times prior to conditioning. Finally, we will discuss recent research that suggests that the participation of some cortical and subcortical structures (including the amygdala) in the influence of several contextual stimuli (such as the spatial context or time of day in the sleep/wake cycle) on the acquisition of CTA and latent inhibition of CTA. With this we hope to highlight some of the possible mechanisms of taste learning in which the different amygdaloid nuclei seem to have a specific function.

2. Amygdala and conditioned taste aversion learning

This section will review the studies that implicate the amygdala in taste learning processes [12]. First, a brief description of the phenomenon of CTA will be provided. Then we will analyse the research that points to the amygdala and its nuclei as part of the brain mechanisms of CTA.

2.1. Description of the conditioned taste aversion paradigm

Conditioned taste aversion learning is a particular conditioning paradigm which exists for the subject to associate the consumption of a new taste with a visceral disease that occurs after. Since a delay usually separates the presentation of the taste from the visceral disease, it is suggested that the learning results from the association between the memory trace of that taste and the disease [13]. The CTA learning is vital for numerous species because the learned aversion could reduce the probability of re-experiencing the toxic effects of a harmful substance. Even though this is a conditioning process, it has some special features when compared to most other forms of associative learning. Taste aversion learning is a paradigm widely used in animal research exploring the brain mechanisms of learning and memory [14]. Therefore, we will describe the taste aversion learning paradigm, which was mainly shown in animals. In humans, CTA has also been studied to a much lesser extent than in animals. For example, taste aversion learning has been examined in humans in order to understand the neurobiology of eating behaviour. Studies using positron emission tomography (PET) have shown that the amygdala and orbitofrontal cortex are activated when processing an aversive taste stimuli [15, 16]. Recent research with functional magnetic resonance imaging (fMRI) in humans has confirmed the involvement of the orbitofrontal cortex, anterior cingulate cortex, insular cortex and amygdala in processing highly aversive flavours [17]. Since the amygdala also seems to be involved in conditioned taste aversion in humans, it is possible that the acquisition of this learning requires biological mechanisms that are common in different species of vertebrates [18]. Moreover, because the food aversion associated with chemotherapy treatment is similar to the experimentally induced taste aversion [19], the CTA paradigm has helped to develop different strategies for dealing with the taste aversion that occurs in patients being treated with chemotherapy [20].

A crucial role in food selection processes is the ability to learn taste aversions [21]. This is particularly relevant for omnivorous species. The discrimination process between edible and harmful, or even potentially deadly, substances starts from the gustatory sensory information. This information stimulates a biological mechanism of precaution against new flavours, which facilitates the evaluation of the consequences of the ingestion of novel substances [22] and subsequently promotes the acquisition of conditioned taste aversions or preferences [8]. The initial response of caution is accompanied by a lower consumption of the novel substances. This phenomenon is called neophobia. If the sensory characteristics of the novel substance are associated with negative visceral consequences (such as poisoning), the animal will then acquire an aversion to that particular taste [23]. If the intake is

associated with a positive visceral consequence (as in the case of an energetic food), or non-aversive, the new flavour will be recognized as being safe. Evolution has resulted in the development of neural mechanisms of attention, motivation, learning and memory that allow such identification of edible substances to be made.

Conditioned taste aversion paradigm exhibits three important features of associative learning; each feature exists separately in other classical conditioning paradigms. First, CTA can be acquired with a single pairing between the taste and the visceral discomfort [6, 13, 22-25]. Second, conditioned taste aversion is an example of a biological predisposition to associate certain stimuli more easily. For example, the taste-illness association occurs more easily than sound-disease or odour-disease associations [26]. The third characteristic of CTA learning refers to the delay that separates the presentation of the taste and visceral stimuli, or absence of temporal contiguity. The association between a new taste (the conditioned stimulus -CS-) and visceral consequences following its ingestion (the unconditioned stimulus -US-) results in a subsequent aversion to that taste, even though a delay of minutes or even hours (far superior to that seen in any other type of associative learning) is used. This unusual property of CTA to resist to a long inter-stimulus delay is related to the physiological processes of digestion. Indeed, in physiological conditioning, a delay always separates the ingestion from a potential poisoning. This delay is necessary for the completion of gastric digestion which results in the transport of nutrients through the gastrointestinal system and the gradual absorption of the products of digestion. Consequently, the association between gustatory and visceral stimuli must comply with this temporal requirement [27].

The experimental procedure used to induce conditioned taste aversion is a tool that has been used for decades in research into learning and the biological substrates of learning and memory [6, 11, 13, 14, 24, and 28]. In the laboratory, the procedure involves water deprivation with limited access to a daily amount of water, or water limited to a restricted time period within the day (usually 15 minutes). Once the daily amount of water consumed is stabilized, the animals receive the presentation of a new taste (representing the conditioned stimulus, generally a saccharin solution dissolved in water at 1%) during the conditioning session. The consumption of this taste is followed twenty or thirty minutes later by a gastrointestinal distress (representing the unconditioned stimulus, generally induced by an intraperitoneal injection of lithium chloride (LiCl), although some other aversive agents [29-36] have been used to induce aversion). Forty eight hours after conditioning, CTA tests can be used to detect the strength of the aversion to the CS previously paired with the malaise [37]. The reduction in the consumption of the CS after learning indicates more than a conditioned avoidance response. In fact, the learned aversion to taste really involves a change in the incentive properties of that stimulus, with its hedonic value becoming repulsive [38]. This learning is easily reproduced in the laboratory, and has proven to be a relevant paradigm for discovering important aspects of the neurobiological substrate involved in associative learning and memory. The following section will describe the findings that appear implicate the amygdala in the acquisition of this kind of learning.

2.2. Amygdaloid nuclei and acquisition of CTA

Conditioned taste aversion learning depends on a complex neural circuit that includes brainstem areas, as well as subcortical and cortical mechanisms [8, 11, 39, and 40]. Lesion studies have provided important information about the different structures and regions of the brain involved in the acquisition of taste aversion [10, 18, 41, 42-44]. The processing of sensory information necessary for the acquisition of a taste aversion involves multiple systems. The taste system detects information from the lingual papillae and palate via the cranial facial nerve (VII), glossopharyngeal (IX) and vagus (X) [8]. The visceral sensory system receives information via the vagus nerve and area postrema of the brainstem [45]. The information from both sensory systems are transported separately to the primary relay brainstem nuclei (nucleus of the solitary tract) and secondary relay (parabrachial nucleus), as well as to brain structures involved in processing visceral and taste, such as the thalamus, the insular cortex and the amygdala [46]. The processing of taste qualities [47] and subsequent association with the visceral effects of toxicity [48-50] requires complex neuroanatomical relationships in which the amygdala seems to be involved [51].

The amygdala and other cortical and subcortical areas are related to the brainstem associative processes necessary for taste aversion conditioning [41, 52-57]. In reference [52], the blockade of protein synthesis or beta-adrenergic receptors in the central amygdala blocks acquisition but not extinction of CTA. The same procedure in the basolateral amygdala blocks extinction but not acquisition of this learning. The authors of this research argue that the neural circuit that makes the acquisition of taste aversion memory possible and the extinction of the aversion requires the activity of the amygdala. However, the involvement of the amygdala and other structures in the associative processes of CTA has been studied by examining protein synthesis associated with learning. In one research it has been observed that the long-term aversive taste memory requires protein degradation in the insular cortex and the amygdala [56]. The selective involvement of the amygdala in CTA has also been analysed in other ways in animal models. There are studies of receptor expression during taste aversion learning [58, 59], studies of the c-Fos expression [60] and other genes [61] in the amygdala, studies of receptors blockade of the amygdala [62] and numerous studies using brain lesions [63], all in the CTA paradigm. For example, possible changes of the leptin receptor expression in the basolateral amygdala in relation to CTA acquisition have been analyzed [59]. Leptin receptor mRNA in the brain was analyzed by *in situ* hybridization and the expression of this receptor was assessed by immunohistochemistry method. Both measures were significantly higher after the formation of CTA. The authors concluded that the amygdaloid leptin receptor is involved in neuronal communication for CTA formation. Other studies [62] have also implicated other amygdaloid receptors in CTA, particularly the noradrenergic receptors. The researchers administered selective bilateral microinfusions of the beta-adrenergic antagonist propranolol into the basolateral amygdala immediately before intraperitoneal LiCl injections. This procedure disrupted CTA memory and the authors proposed that the basolateral amygdala is a critical structure in modulating the consolidation of taste memory. Genetic studies have confirmed the relation between amygdala and CTA. In this regard, studies have recently identified some specific genes in

the amygdala (associated with neuropeptides, G protein-coupled receptors, ion channels, kinases and phosphatases) that contribute to CTA acquisition [61].

Regarding the lesion procedure; the studies that describe a lesion in the amygdala have not been decisive so far as they have shown a weak effect on taste learning or even no effect at all. However, electrolytic lesions of amygdala were shown to attenuate or disrupting CTA [64, 65] and also been shown to affect the neophobia phenomenon [65, 66]. Taken together with other studies that reported a selective involvement of the basolateral nucleus in CTA [67], it has been suggested that the effect of the basolateral injury on CTA is due to an alteration of the proper appreciation of the gustatory signal novelty, which could have affected the subsequent expression of taste aversion [63,68]. Subsequent studies have confirmed this hypothesis by reporting a selective effect on CTA [69] or a dual effect on neophobia and taste aversion [70] after basolateral nucleus lesion.

Moreover, electrolytic lesioning of the basolateral nucleus of the amygdala did not induce any effect on the formation of taste aversion in different studies [71-73]. Some authors have argued that the involvement of the basolateral amygdala in CTA is indirectly mediated by its interactions with the nucleus of the solitary tract [74] or the insular cortex [71, 72] therefore showing that the electrolytic lesions indirectly affects the acquisition of taste aversion. Nevertheless, other brain manipulation tools and neurophysiological techniques have also implicated the basolateral nucleus of the amygdala in the acquisition of CTA learning [51, 75-80]. In other studies [51] it has been found that specific neurons in basolateral amygdala respond to convergent taste stimulus and unconditioned stimulus information during CTA. The authors used a procedure of analysis of temporal gene transcription by fluorescence *in situ* hybridization in order to locate these populations of neurons. In [77], it was shown that CTA memory needs protein synthesis in the basolateral amygdala, and in [79] it has been proposed that the basolateral amygdala interacts with the insular cortex to modulate the memory consolidation because the infusions of the beta-adrenergic antagonist propranolol administered into this nucleus blocked the enhancing effects on CTA of a muscarinic agonist infused into the insular cortex.

The local injection of excitotoxic agents (such as NMDA or ibotenic acid) induces a more selective lesion in the cell bodies of the target structure. Although the excitotoxic lesioning of the amygdala has not always resulted in deterioration of CTA [71, 81, 82], the excitotoxic lesions of the basolateral amygdala often reproduce the effects obtained with electrolytic lesion on CTA [10, 44, 50, 83-86]. In contrast, the excitotoxic lesion of the central amygdala does not affect the formation of taste aversion [44, 83, 84, and 87]. The possible role of the central nucleus of the amygdala in CTA seems to be related to the processing of visceral information. For example, immunohistochemistry has found increased levels of a specific protein kinase associated with the memory of CTA in the cells of the central nucleus of the amygdala after injection of a high dose of LiCl-induced visceral malaise (US) [88]. A local microinjection of an inhibitor of this kinase into this nucleus decreased the strength of the CTA as well as the levels of this protein in the central amygdala. The authors of this study proposed that the intracellular levels of this protein kinase in the central amygdala are critical to process the visceral information in CTA. Therefore, it seems that the amygdaloid

nucleus, which is involved in the acquisition of CTA, is the basolateral nucleus. In this regard, an unpublished study conducted in our laboratory has shown that excitotoxic lesions of the basolateral amygdala decreases taste aversion but does not disrupt the learning. In this study we performed bilateral excitotoxic lesions in the basolateral nucleus of the amygdala by local injection of NMDA and compared these animals' learning with two control groups. One was sham-lesioned in the amygdala and one with a lesion in the hippocampus, a structure not involved in CTA. The results showed a learning impairment in the case of animals with a basolateral lesion, compared with both control sham- and hippocampus-lesioned groups (see Figure 1).

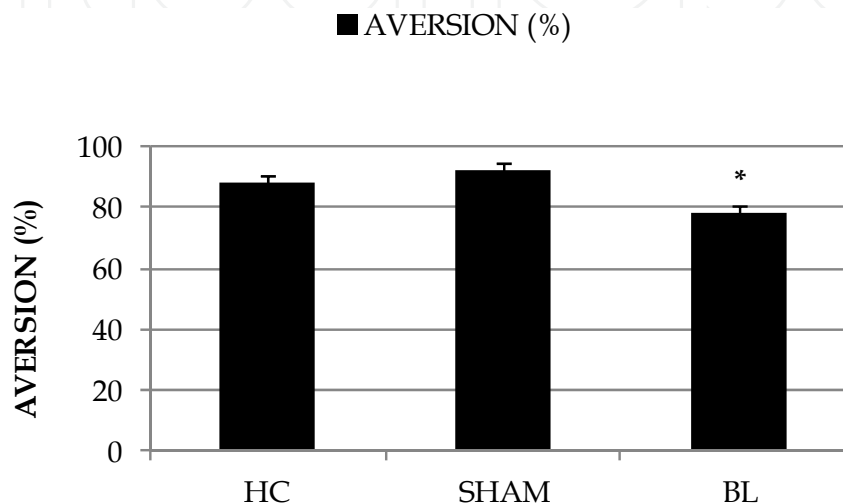


Figure 1. Percentage of taste aversion to saccharin in animals with lesion in the hippocampus (HC) or the basolateral amygdala (BL), as well as in the sham group. The percentage was calculated as a ratio between the saccharin consumed the day of acquisition of learning / saccharin consumed the day of acquisition of learning + saccharin consumed the testing day [X100].

Figures 2 and 3 show stained brain sections of a sham-lesioned animal and an animal with excitotoxic lesion in the basolateral amygdala induced by local injection of NMDA.

These results suggest that the basolateral amygdala is part of the brain circuitry of CTA, but is not a necessary structure for this learning. In other studies, the inactivation of the basolateral amygdala has not disrupted the CTA [89], or has impaired the learning but did not prevent its acquisition [7]. Therefore, our study, which used excitotoxic lesions, is consistent with the hypothesis that the formation of taste aversion does not require the integrity of the amygdala, although it does seem to be an important structure in the modulation of CTA [41] since the selective lesion of the basolateral amygdala reduces, but does not prevent, the learning. The reversible lesion studies also suggest that the amygdala, or any of its nuclei, is involved in the neural mechanism responsible for CTA learning. For example, the inactivation of the amygdala using local microinfusions of tetrodotoxin (TTX) has confirmed the involvement of this structure in the acquisition and recovery of CTA [7, 90].

In summary, the evidence indicates that the amygdala is part of the neurobiology of taste aversion learning [51, 63, and 91]. Although the exact mechanism is unknown, the data

suggest that anatomical and functional relationships between amygdala and insular cortex are necessary for the correct acquisition of conditioned aversion [79, 92]. Research also indicates that the projections from the amygdala to the hypothalamus [93,94] and, in particular, to the brainstem nuclei involved in taste aversion learning [46,74,95-99] also play a significant role in this kind of conditioning.

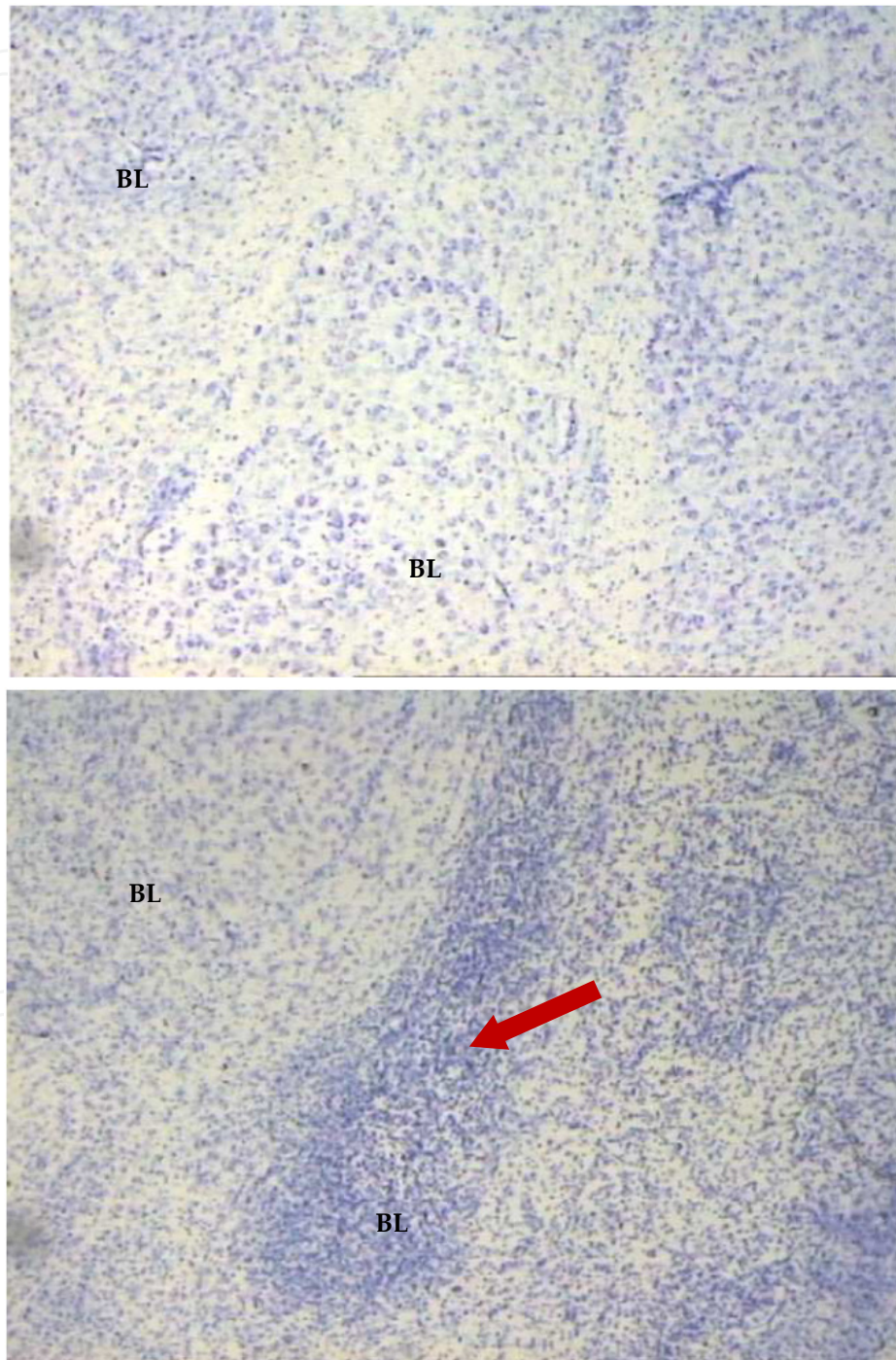


Figure 2. Section of the brain of a sham animal (above) and an animal with excitotoxic lesion in the basolateral (BL) amygdala (below). The arrow indicates the reaction of the microglia in this nucleus of the amygdala induced by the neurotoxin, compared with sham animal (image amplified 40x).

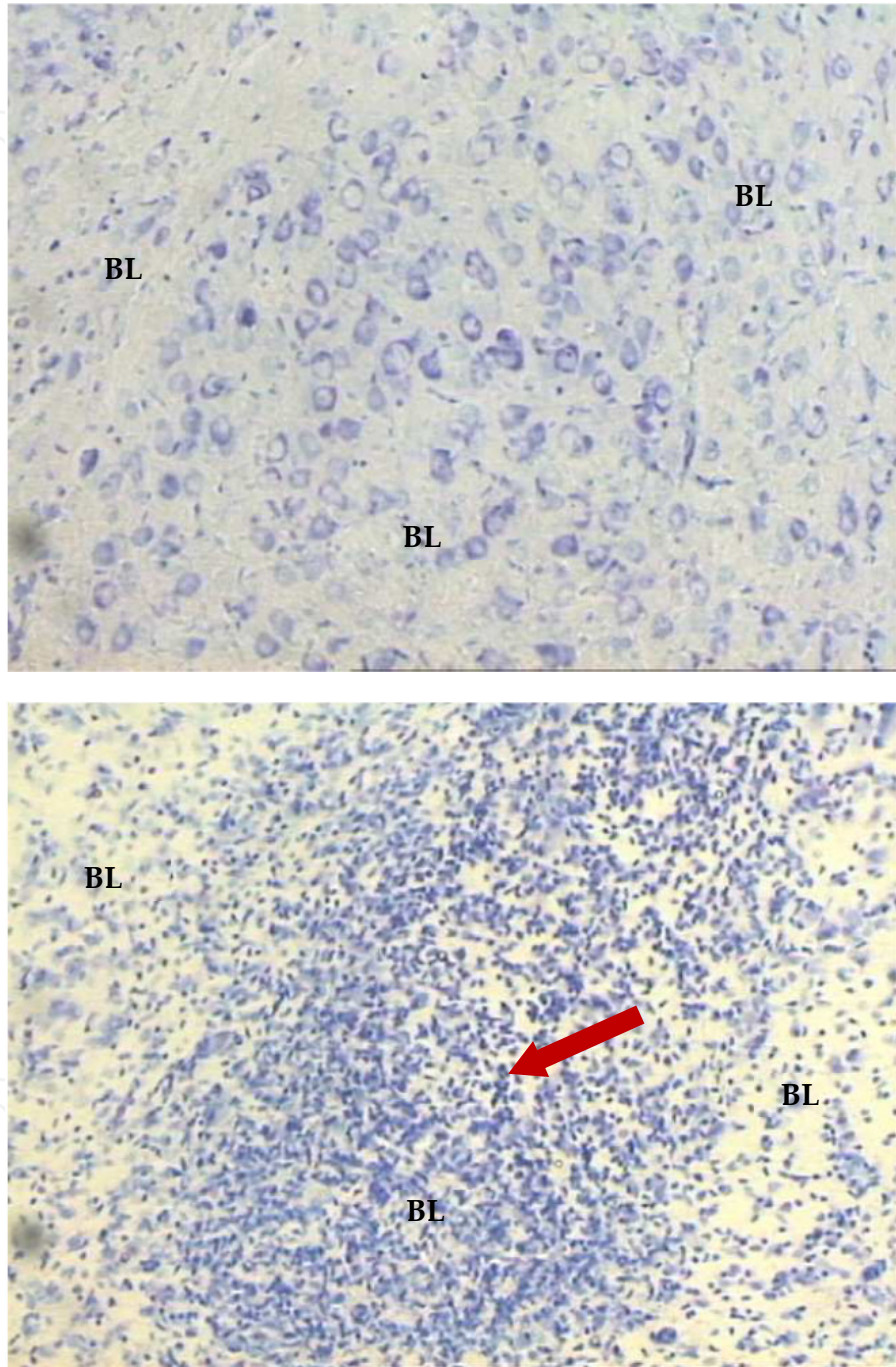


Figure 3. Detail amplified 100x of the sections of the Figure 2.

3. Latent inhibition and amygdala

Latent inhibition refers to a reduction in the conditioned aversion to a stimulus that has been previously pre-exposed without reinforcement. This phenomenon is easily reproduced in the laboratory and is demonstrated by presenting a stimulus several times (for example a sweet solution), which will subsequently be paired with a visceral malaise during one acquisition session. The latent inhibition response results in an absence, or a significant decrease, in the aversive response to the conditioned stimulus during the test session. In the following sections we will describe the phenomenon of latent inhibition in the CTA paradigm, and then review the studies implicating the involvement of the amygdala in the mechanisms underlying this learning.

3.1. Latent inhibition of taste aversion learning

The effect of latent inhibition has been demonstrated consistently in CTA learning [100-105]. Non-reinforced pre-exposure to a particular taste reduces the magnitude of CTA when this taste is subsequently associated with gastrointestinal discomfort. The experimentally obtained latent inhibition (LI) results in a higher aversion to the taste not experienced before the acquisition, in comparison to the aversion to the taste that has been pre-exposed. This reduction in the conditioned response is comparable to that obtained by pre-exposure in conventional experiments of classical conditioning [101,104].

Several cortical areas and subcortical structures have been specifically involved in the neural mechanisms that support latent inhibition depending on the learning paradigm used. For example, latent inhibition of the CTA, the fear conditioning and the cued fear conditioning, the eye blink response and some appetitive conditioning [106-114]. Some of the structures and systems involved in latent inhibition are the hippocampus, the mesolimbic dopaminergic pathway, the entorhinal cortex and the nigrostriatal dopaminergic pathway [115]. In addition, the nuclei of the amygdala have also been studied in relation to latent inhibition in several learning paradigms, although in CTA the results do not confirm the involvement of any of these nuclei in this phenomenon [110].

3.2. Amygdala and latent inhibition of taste aversion learning

According to [113], a complex neural circuit involving the connection of the medial prefrontal cortex, the striatum and the amygdala with the nucleus accumbens, is involved in the phenomenon of latent inhibition. The specific role of each component of the circuit could explain the discrepancy between the results obtained with lesions. For example, [114] has reported that electrolytic lesioning of the basolateral amygdala leaves latent inhibition intact in a conditioned emotional response procedure. In contrast, in [116] it was observed that excitotoxic lesioning of the basolateral amygdala interferes with the effect of pre-exposure to a light-food pairing in a reinforcer devaluation procedure. Furthermore, in an appetitive conditioning task it was found that the lesions in the basolateral amygdala disrupted the

latent inhibition [117]. The authors of this research concluded that the connections between the basolateral amygdala and the entorhinal cortex are crucial in the formation of latent inhibition. Molecular biology has also provided extensive information that suggests the involvement of the amygdala in latent inhibition depends on NMDA receptors. Blockade of these receptors in the basolateral amygdala by selective antagonists prevents the expression of latent inhibition in a fear conditioning task [118]. Moreover, it has been found that excitotoxic lesioning of the central amygdala does not affect the latent inhibition in a Pavlovian appetitive conditioning task [119] or a reinforcer-devaluation procedure [116]. Nevertheless, [120] observed an intense production of c-Fos protein in central amygdala neurons (which is associated with intense cellular activity), which correlated with the decrease in the conditioned response to a familiar stimulus. Therefore, although the real function of the amygdala in latent inhibition is still being researched, the data appear to suggest some involvement of the basolateral amygdala in this learning. These findings also seem to confirm that the regions involved in the brain circuit that support the latent inhibition process may be different, depending on the type of conditioning used.

Experiments on latent inhibition in CTA have not yet permitted us to define the neural mechanisms supporting the learning processes of this paradigm, although CTA is probably the paradigm that has provided the most documented information about the neurobiology of latent inhibition. The hippocampal lesion studies have attempted to demonstrate the involvement of this structure in latent inhibition but the results have not been decisive. For example, in reference to [121] it has been observed, by computer simulations, that depending on the behavioural protocol (particularly the total time of pre-exposure), the perception of novelty after hippocampal lesion could be larger, equal to, or smaller compared to the novelty in control animals. In contrast, the striatum has been clearly involved in latent inhibition of taste aversion learning [111, 122]. Regarding the amygdala; lesions of the basolateral nucleus have also not shown detrimental effects on latent inhibition of conditioned taste aversion [123]. In latent inhibition of CTA, the dopaminergic system of the basolateral amygdala has also been examined and has shown that dopamine in this nucleus does not appear to modulate the latent inhibition but rather the phenomenon of prepulse inhibition [110].

In order to test the involvement of the amygdala or the hippocampus in latent inhibition of CTA, we tested the effect of bilateral excitotoxic lesions of both structures in this paradigm. The results of this study showed that neither lesion of the amygdala (mainly located in the basolateral nucleus) nor hippocampus affected latent inhibition of CTA (see Figure 4).

Figures 5 and 6 show stained animal brain sections with excitotoxic lesion in the hippocampus or the basolateral amygdala, respectively, induced by local injection of NMDA.

Taken together, the results of this study indicate that the expression of latent inhibition in taste aversion learning paradigm does not require the participation of the hippocampus or amygdala.

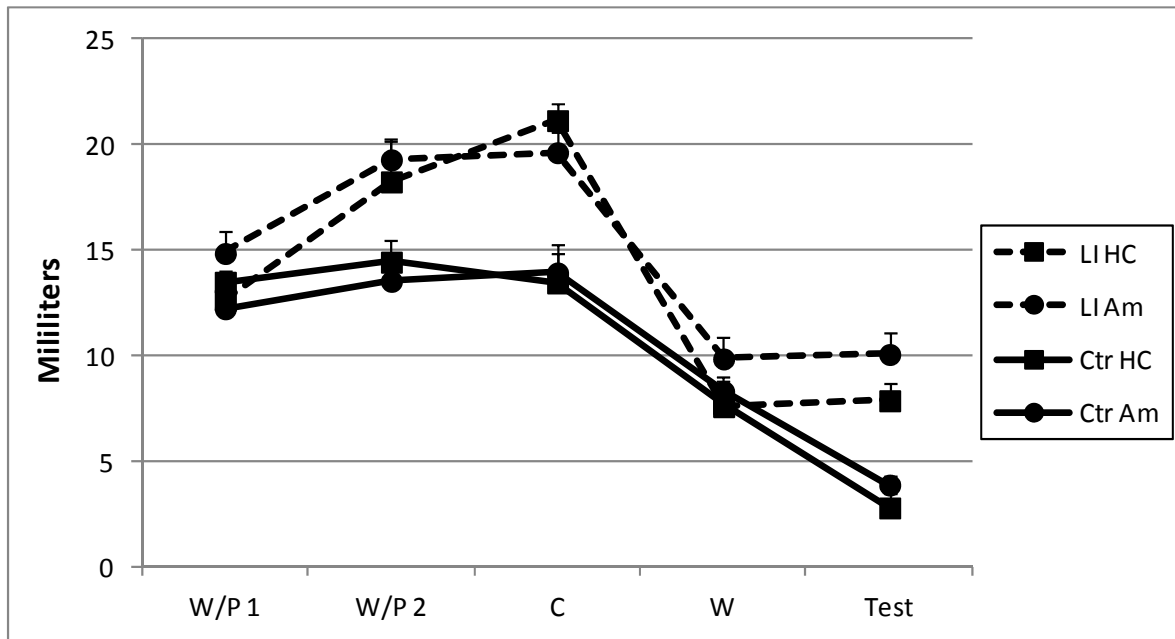


Figure 4. Representation of the average quantity of fluid in milliliters ingested by each of the groups (latent inhibition -LI- and control -Ctr-, with lesion in hippocampus -HC- or amygdala -Am-) over the days (W/P = water vs. pre-exposure to saccharin -CS-; C = conditioning; W = recovery with water; Test).

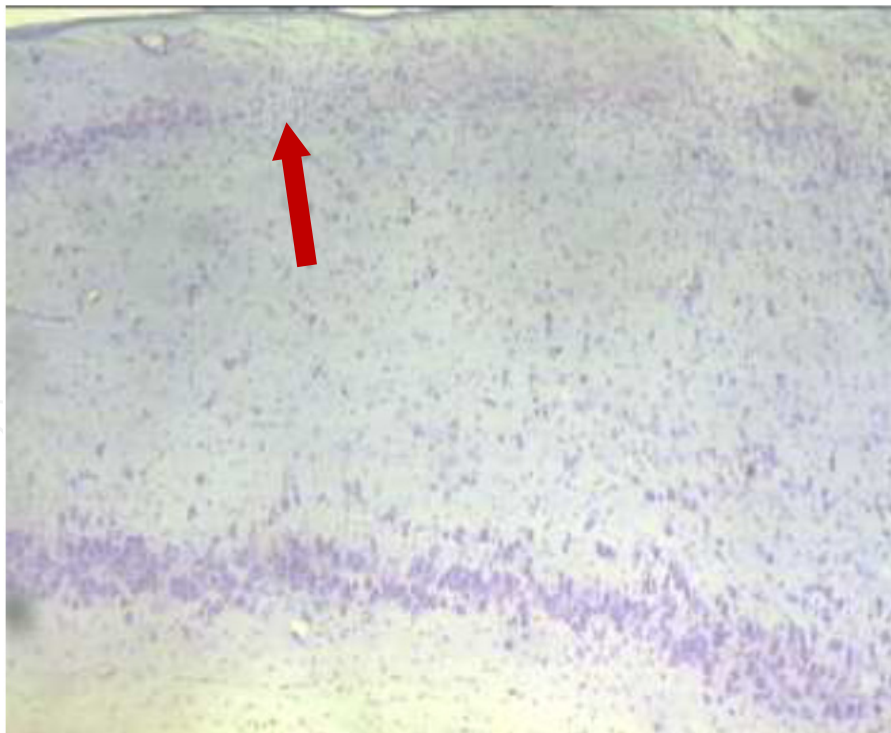


Figure 5. Section of the brain of an animal with excitotoxic lesion in the hippocampus. The arrow indicates the neurodegeneration of the CA1 hippocampal region induced by the neurotoxin (image amplified 40x).

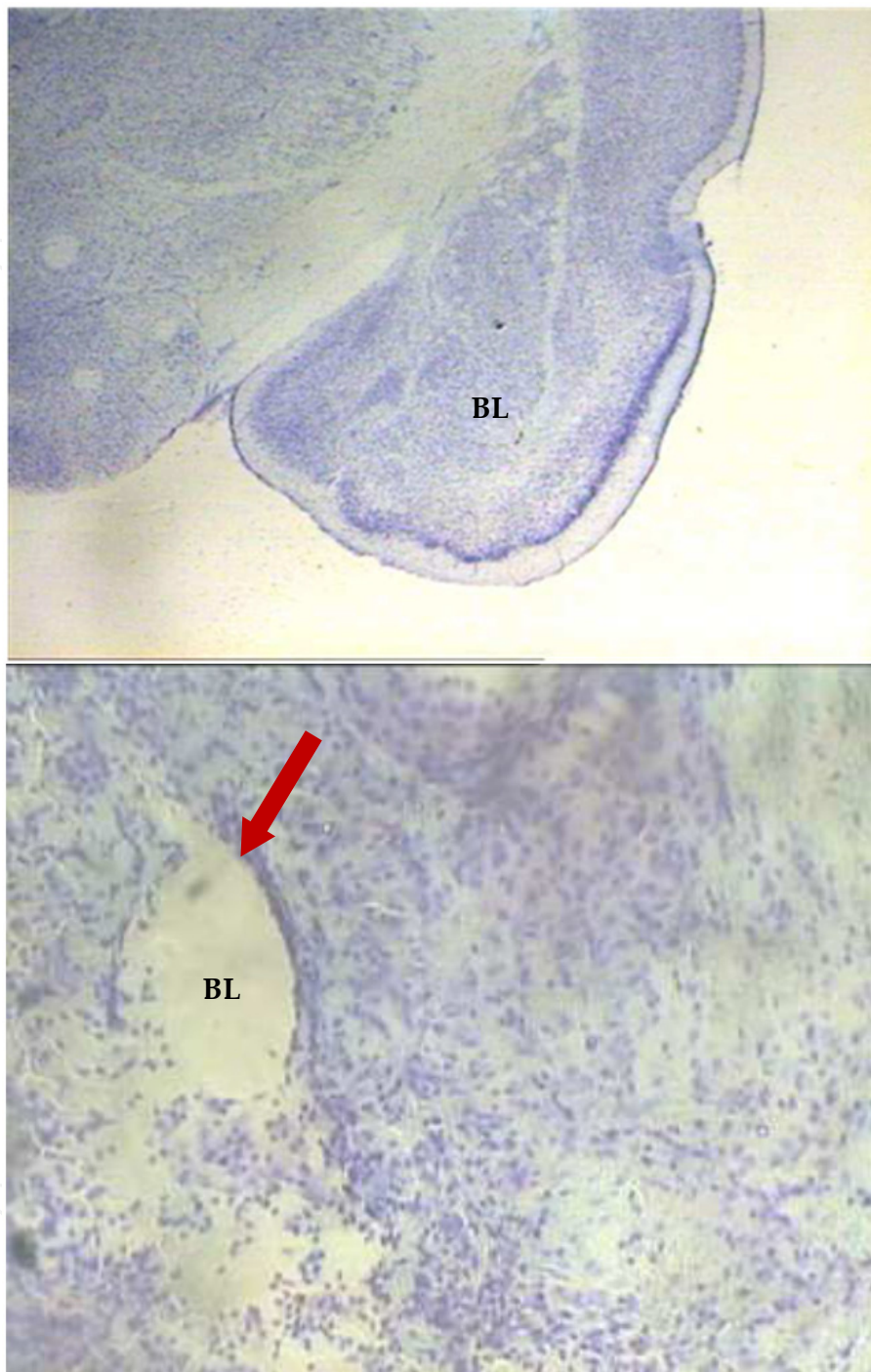


Figure 6. Section of the brain of an animal with lesion in the basolateral nucleus (BL) of the amygdala (above). Below, the arrow indicates the neuronal loss induced by NMDA in the basolateral amygdala (image amplified 40x).

4. Context, taste learning and amygdala

Contextual cues can modulate the conditioned response in numerous paradigms of learning. The brain mechanisms supporting this contextual effect on learning are not fully known.

The research indicates that the hippocampus and the amygdala participate in a different way in the context-learning relation, depending on the contextual cues and the behavioural paradigm used. The following sections will review the effects of context on learning and describe the involvement of the amygdala and hippocampus in the contextual modulation process of taste learning.

4.1. Effects of context on taste learning

Different contextual cues, both physical and interoceptive, can influence the processes that lead to associative learning [124-126]. The most explored contextual cue is the spatial context, represented by the physical characteristics of the experimental box [124,127]. For example, latent inhibition of fear conditioning [128] and latent inhibition of CTA are sensitive to the effects of a change in spatial context [101, 129, and 130]. Similarly, taste aversion learning [131] and its extinction [132] are also sensitive to the spatial context of learning. However, the influence of temporal context in associative processes is also a good model for understanding the mechanisms of learning and memory [133]. Regarding the modulating effect of time of day, we have shown in our laboratory that the time of day in the sleep/wake cycle acts as a contextual cue and modulates latent inhibition of taste aversion learning [134] and CTA retrieval [135].

The neurobiological processes underlying contextual effects on associative learning may vary depending on the characteristics of the contextual cues involved and the learning paradigm used. In this sense, the hippocampus and the amygdala appear to be specifically involved in the contextual effects on conditioning, depending on the type of learning paradigm. The hippocampus seems to be involved in memory processes and contextual learning [136], mainly in the paradigm of fear conditioning and in spatial tasks, such as the Morris water-maze [137-139]. Some reports also suggest that the amygdala is part of the brain mechanism that allows the context to influence fear conditioning [140-142] and place conditioning [143]. The amygdala appears to be an important structure involved in the effects of context on other forms of associative learning, for example, on conditioned potentiation of eating [144]. The next section will evaluate the role of the amygdala and hippocampus in the modulating effects of context on taste learning.

4.2. The limbic system and the effect of context on CTA

The spatial context dependency of the latent inhibition phenomenon appears to involve the activity of the hippocampus [120,121,145,146]. Temporal context dependency also seems to be mediated by the hippocampus in the paradigm of latent inhibition of taste aversion learning [147], as well as in CTA [14]. However, no studies have reported the role of the amygdala in the temporal modulation of taste learning [134,135]. It is possible that the amygdala is involved in CTA selectively but not in the phenomenon of latent inhibition in this paradigm, nor in the contextual dependency of this phenomenon. This possibility can be contrasted with the apparent involvement of the hippocampus in the contextual effects on latent inhibition of CTA [147], but not in taste aversion learning. To elucidate this

differential involvement of both structures, we have performed some experiments aimed at evaluating the effect of a change in temporal context between pre-exposure and conditioning in animals with bilateral excitotoxic lesion in the amygdala or the hippocampus. These groups were further divided into two subgroups, one consisting of animals pre-exposed to the taste (CS) and conditioned at the same time of day (groups “same”) and the other one pre-exposed and conditioned at different times of day (groups “different”).

Figure 7 shows the consumption of animals throughout the behaviour procedure. All groups were pre-exposed and conditioned in different temporal contexts (groups “different”) consumed significantly less (except the group with hippocampal lesion) that the “same” groups in test days. Therefore, a change in the time of day between pre-exposure and conditioning disrupted the latent inhibition learning of CTA. Nevertheless, the group with lesion in the hippocampus did not show this temporal context specificity, and the consumption of these animals after conditioning was similar to that of the “same” groups.

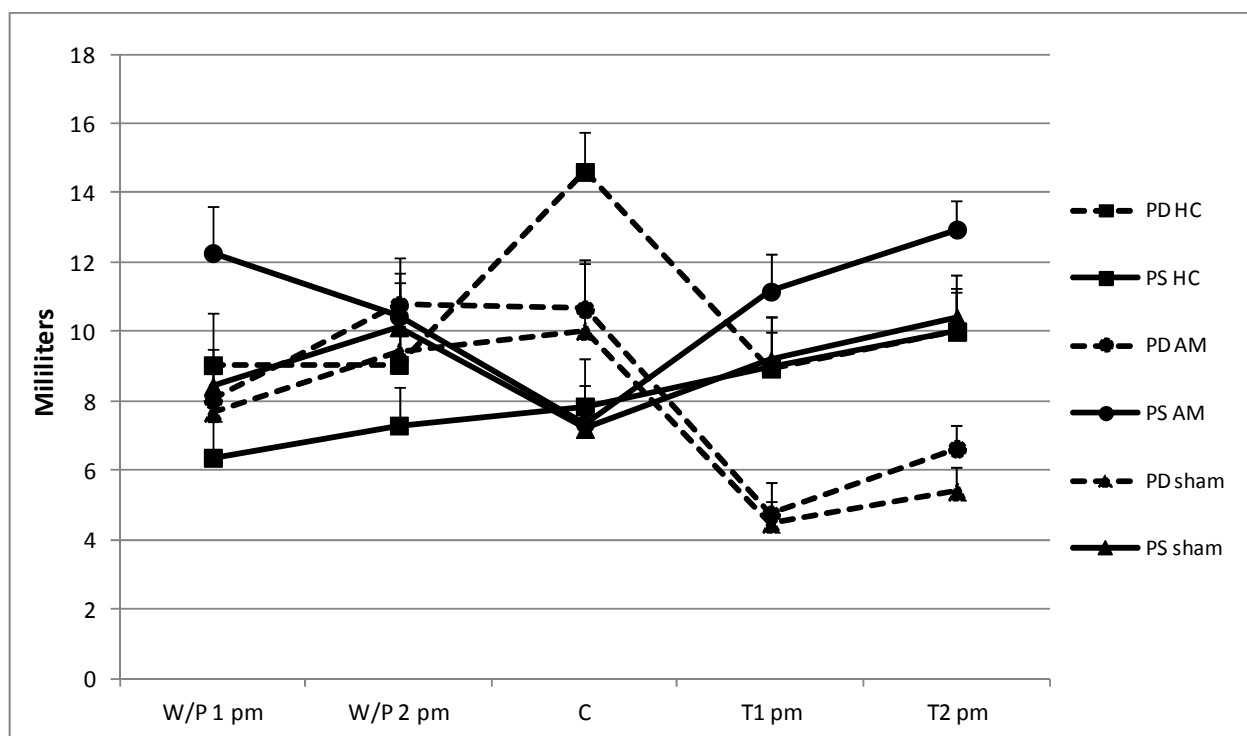


Figure 7. Representation of the average quantity of fluid in millilitres ingested by each of the groups (pre-exposed different -PD- and pre-exposed same -PS-, with lesion in hippocampus -HC- or amygdala -Am-, and pre-exposed different -PD- and pre-exposed same -PS- sham groups) over the days (W/P 1-2 pm = water vs. pre-exposure to saccharin in the evening session; C = conditioning in the morning -different- or evening -same- sessions; T1-2 pm= tests 1 and 2 in the evening session).

Figures 8 and 9 show stained brain sections of animals with NMDA-induced excitotoxic lesion in the hippocampus or the basolateral amygdala, respectively, compared with sections of sham animals.

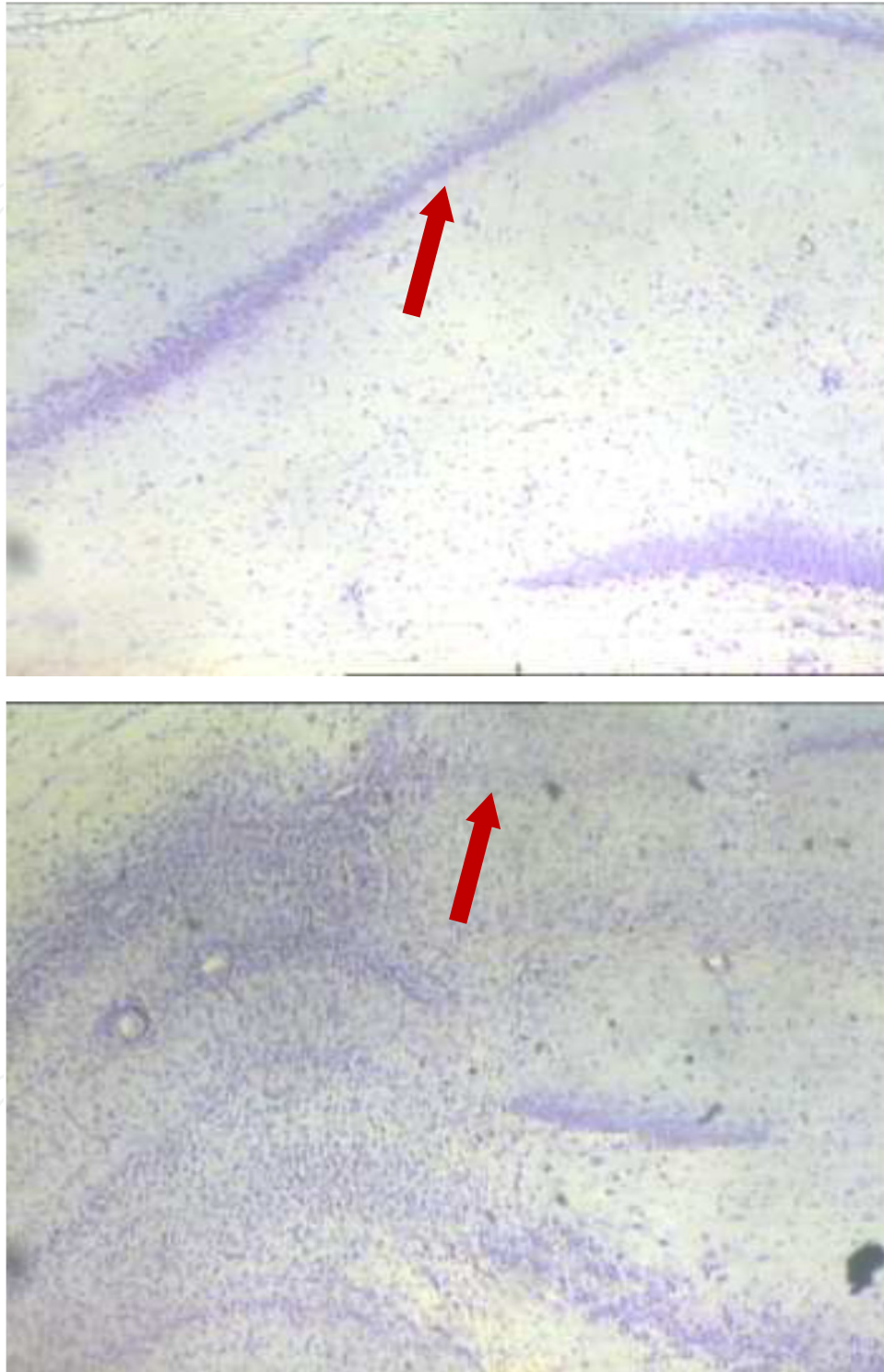


Figure 8. Section of the brain of an animal with sham lesion in the hippocampus (above). The arrow indicates intact cells of the CA1 hippocampal region. The bottom panel shows a section of the brain of an animal with hippocampal lesion. The arrow shows the destruction of the cells of the CA1 hippocampal region induced by the neurotoxin (images amplified 40x).

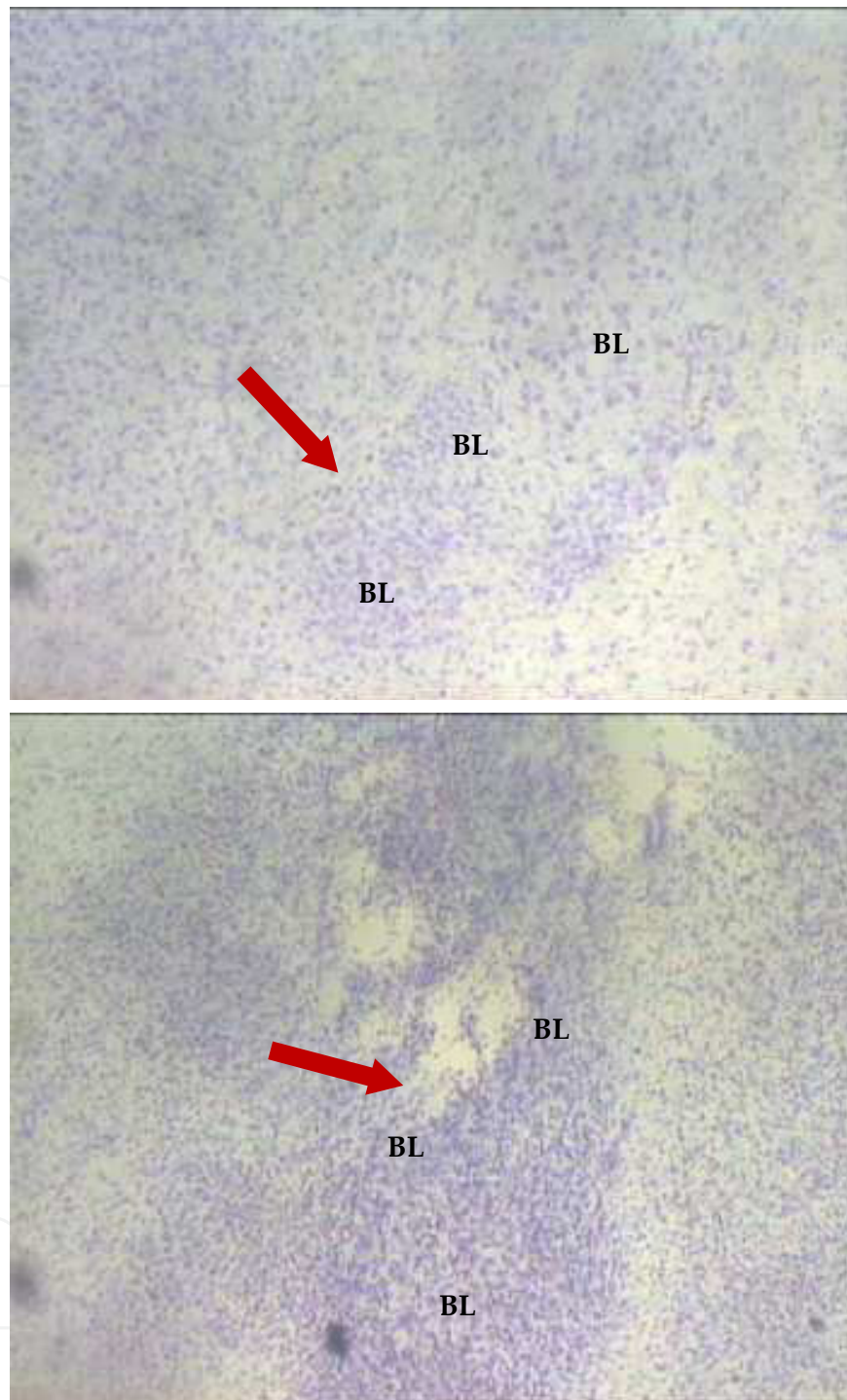


Figure 9. Section of the brain of an animal with a sham lesion in the basolateral (BL) amygdala (above). The arrow indicates intact cells of this nucleus. The bottom panel shows a section of the brain of an animal with lesion in the basolateral (BL) amygdala. The arrow shows the destruction of the cells of this amygdaloid nucleus induced by the neurotoxin (images amplified 40x).

In summary, our studies have shown that the hippocampus is necessary for the temporal specificity of latent inhibition of taste aversion learning, but not the amygdala. Subsequent studies performed in our laboratory have shown that the lesion in the hippocampus does

not affect the phenomenon of latent inhibition in the CTA paradigm, confirming the selective function of this structure on the effects of a change of context on the phenomenon of latent inhibition of taste aversion learning. On the contrary, the amygdala is involved selectively in the acquisition of taste aversion, but not in the complex phenomena of latent inhibition and contextual modulation of taste learning.

5. Conclusions

The amygdala is a limbic structure involved in various processes of associative learning. Specifically, research has shown that the amygdala is part of the brain mechanism of taste aversion learning [11, 24, 41, 67, and 75]. Its role in aversive taste memory, however, is not entirely clear. Apparently, the taste memory trace requires the activity of the insular cortex [148]. The association between gustatory and visceral stimuli takes place in the brainstem [11, 41, 44, 60], although the consolidation of the memory of the association certainly seems to imply other structures such as the insular cortex or the amygdala [149]. The functional connections between the insular cortex and amygdala [92], and between the visceral processing nuclei and the amygdala [88], mean it is possible that the involvement of this structure or any of its nuclei in CTA is limited to a modulatory function, either of the sensory processing or the association between stimuli and its recovery [67]. This could explain the data obtained in some studies that shows amygdaloid lesion or its inactivation does not disrupt learning. In our study, excitotoxic lesion altered the acquisition of CTA but did not prevent learning, which may suggest that the amygdala regulates the associative process or the associative memory retrieval once established. Amygdaloid activation observed in different studies in the CTA paradigm [58, 59, and 61] is consistent with this proposal and supports the idea that the amygdala is an active structure in the acquisition of CTA but is not necessary to establish the association between stimuli or for the recovery of the association. The modulatory effects of the amygdala on learning and memory have also been described in studies of working memory and memory consolidation and extinction [150], consolidation of emotional memory [151], sensory memory representations in the cortex [152], acquisition of avoidance reactions [153], and CTA [149], among others.

The different effects on the magnitude of aversion resulting from the manipulation of the amygdala can be attributed to the particular mediation of the neophobia phenomenon in taste aversion, as well as the specific technique and procedure used. Nevertheless, in general, lesioning or inactivation of the amygdala does not prevent the CTA but reduces the magnitude of taste aversion. It seems, as described above, that the amygdala is a structure relevant for the correct acquisition of taste aversion. In this respect, our studies have shown that the excitotoxic lesioning of the amygdala does not eliminate CTA learning but decreases the acquired aversion. However, studies into the involvement of the amygdala in taste learning complex phenomena suggest that this structure is not decisive for the acquisition of latent inhibition of taste aversion learning [123], nor has its participation in the effects of spatial or temporal context on this phenomenon been demonstrated. Our experimental data support the hypothesis that the amygdala is selectively involved in the acquisition of taste

aversion but not in the phenomenon of latent inhibition of taste aversion learning, nor in the contextual dependence of this phenomenon. In contrast, another structure of the limbic system, the hippocampus, does not seem to be involved in conditioned taste aversion nor in latent inhibition of this learning [121]. However, our experiments have shown that the contextual dependency of latent inhibition of taste aversion learning requires the integrity of the hippocampus [147], even when this structure is not necessary for the acquisition of latent inhibition in taste aversion learning paradigm. These findings demonstrate the differential functions of the amygdala and hippocampus in taste learning.

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