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Effects of extensive amygdaloid lesions on conditioned taste aversion in rats

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The role of the amygdala in the acquisition of conditioned taste aversion (CTA) is unclear. The lesion studies that have explored specific nuclei of the amygdala point to a probable involvement of the basolateral amygdala, but it remains unclear whether the function of the amygdala in CTA is limited to the activity of the basolateral amygdala. In the current study, extensive bilateral lesions of the amygdala were performed in Wistar rats to explore if the destruction of the amygdala affects the acquisition of CTA, as has been reported with selective lesions of the basolateral amygdala. The magnitude of the taste aversion of animals with extensive lesions of the amygdala was compared with those of animals with similar lesions of the striatum (a structure apparently unrelated to CTA) and animals without lesions. Taste aversion was analyzed by the one-bottle test and two-bottle choice test. The results of the one-bottle test indicated that amygdaloid lesions significantly reduced the magnitude of taste aversion compared with that of animals without lesions. Animals with lesions of the amygdala also showed a greater preference for the conditioned taste stimulus, but this preference did not reach statistical significance. Besides the effect on CTA, animals with amygdaloid lesions showed no evidence of taste neophobia on the day of conditioning. These findings suggest that amygdaloid lesions may affect CTA by disrupting the perception of novelty during conditioning in a manner similar to the effect reported with basolateral lesions.

Key words: amygdala, conditioned taste aversion, neophobia, rats, striatum

INTRODUCTION

The neural mechanism of conditioned taste aversion (CTA) includes the brainstem and subcortical and cortical areas (Bielavska and Roldan 1996, Yamamoto and Ueji 2011). The amygdala is one of the structures believed to be involved in CTA (Bermúdez-Rattoni and Yamamoto 1998, Scott 2011), although it has not been elucidated whether the activity of the amygdala, or some of its nuclei, are necessary for the acquisition of this learning. Significant differences with respect to lesion size and the specific procedure for testing taste aversion have contributed to the current uncertainty about the relevance of the amygdala for the acquisition of CTA. Thus, reported electrolytic and excitotoxic lesions have mostly included the basolateral and central nuclei of the amygdala (Reilly 2009). Lesions including both nuclei have resulted in both an abolition and reduction of taste aversion (Morris et al. 1999, Reilly and Bornovalova 2005). Non-significant effects on CTA with extensive lesions of the amygdala have also been reported (Bermúdez-Rattoni and McGaugh 1991). Several tests have been used to assess taste aversion in lesion studies, such as one-bottle tests (Morris et al. 1999) or two-bottle choice tests (Sakai and Yamamoto 1999). The results of both tests are differently influenced by the deprived state of the animals. In addition, the aversion measures from one-bottle tests may show different results if the quantities recorded on the test day are analyzed independently of the conditioning day or if estimates of consumption are made in relation to the amount ingested on the conditioning day (Bernstein 1999, Bures 1998).

The multitude of afferent and efferent connections of the amygdala make this structure a suitable place to integrate diverse information and modulate, thus the acquisition of taste aversion. Afferent fibers to the baso-

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lateral amygdala from the nucleus of the solitary tract (NTS) have been involved in the visceral pathway that is activated during the acquisition of CTA (García-Medina et al. 2015, Spray and Bernstein 2004). The connectivity between the basolateral amygdala and the insular cortex is also believed to be part of the neural mechanism implicated in the acquisition of CTA (Bermúdez-Rattoni et al. 2004, Guzman-Ramos and Bermudez-Rattoni 2012, Miranda et al. 2003, Miranda and McGaugh 2004, Reilly 2009). However, it is unknown whether the amygdala has a function in the acquisition of CTA that is limited to the activity of the basolateral amygdala. For example, reduced taste aversion has recently been reported after selective lesions of the basolateral amygdala using the one-bottle test and when comparing consumption on the test day with consumption on the day of conditioning (Molero-Chamizo 2017). The results indicated that animals with lesions of the basolateral amygdala acquired CTA, although both measures showed a reduced taste aversion after these selective lesions. It would be interesting to explore the effects of extensive amygdaloid lesions, including not only the basolateral amygdala, but also the central and medial nuclei, in order to determine whether, through different measures (one-bottle tests and two-bottle choice tests), the reduction in the magnitude of the taste aversion increases. This could help in clarifying if the effects of amygdaloid lesions depend on the specific damage induced in some of their nuclei.

Therefore, the aim of this study is to analyze the effects of extensive amygdaloid lesions on the acquisition of CTA by using both taste aversion tests.

METHODS

Subjects

Twenty-three adult male Wistar rats, weighing between 270-300 g, were individually housed in boxes measuring 30 cm×15 cm×30 cm throughout the behavioral procedure. All animals were exposed to a 12-hour light-dark daily cycle (lights on from 9:00 to 21:00), and the temperature was kept constant at 23°C. Food was provided ad libitum, and the availability of fluid was restricted to 15 min daily throughout the behavioral procedure. The study was approved by the Ethics Committee for Animal Research of the University of Granada. It was conducted in strict accordance with both the National Institutes of Health Guide (United States) for the Care and Use of Laboratory Animals (2015 revision, Office of Laboratory Animal Welfare, Health Research Extension Act of 1985, Public Law 99-158, November 20, 1985, "Animals in Research") and the European Community Council Directive 2010/63EU. All possible attempts were made to minimize the effects of the procedure on health of the animals, in accordance with the standards of previous lesion studies in this paradigm (Bermúdez-Rattoni and Yamamoto 1998, Reilly 2009, Yamamoto et al. 1995).

Surgery

The rats were randomly distributed into the following three groups: Amygdala, animals with extensive amygdaloid lesions (*n*=8); Striatum, animals with extensive striatal lesions (*n*=8); IC, intact control animals without lesions (*n*=7). Each animal was anaesthetized with an intraperitoneal injection of sodium pentobarbital (50 mg/kg), which induces anesthetic effects but does not induce acesodynous effects, and then placed in a stereotaxic apparatus for surgery (Stoelting Co. Instruments, Wood Dale, IL, USA). The incisor bar was set at 3.3 mm below the interaural line. After a longitudinal scalp incision was made to expose the skull, the bregma and lambda points were leveled in the horizontal plane, and five trepanations were made in each hemisphere for each animal, using bregma as a reference point to induce lesions in the amygdala or the striatum. The stereotaxic coordinates used to locate the areas of the lesions (Table I) were taken from the atlas of Paxinos and Watson (2005).

Table I. Stereotaxic coordinates.

Group	Axis	Lesion 1	Lesion 2	Lesion 3	Lesion 4	Lesion 5
Amygdala	A-P	-2.3	-2.3	-2.8	-2.8	-3.3
	M-L	±4.5	±3.5	±5.0	±3.8	±5.0
	D-V	+8.4	+9.2	+8.2	+9.2	+8.8
Striatum	A-P	-0.8	-0.8	-1.3	-1.3	-1.8
	M-L	±3.4	±4.4	±3.4	±4.6	±4.6
	D-V	+5.0	+5.8	+4.8	+5.8	+6.0

A-P, anterior-posterior axis; M-L, medial-lateral axis; D-V, dorsal-ventral axis.

All animals, with the exception of the IC animals, received anodal current (1.5 mA) in each trepanation of each hemisphere for 30 s, using a DCLM-5 lesion generator (Grass Instruments, Quincy, MA, USA). After the lesions were completed, the electrode was removed and the incision was sutured. Then, the rats were allowed a postoperative recovery period of seven days in which water and food were available ad libitum.

Behavioral Procedure

At the end of the postoperative period, all of the animals were deprived of fluid for a daily period of 23 h and 45 min throughout the experiment. The drinking sessions (15 min) and subsequent recordings were performed at 11:00 am. The mean consumptions of water by each group on the five baseline days were recorded. Subsequently, on the conditioning day, all groups were exposed to a sodium saccharin solution (0.1%) for 15 min, and their consumptions were recorded. Twenty minutes later, the animals received an injection of lithium chloride (LiCl; 0.15 M, 2% of body weight, ip) and were then returned to their home boxes. After one day of recovery with water (also available for 15 min), all the animals were exposed again to saccharin for 15 min (by the one-bottle test), and their consumptions were recorded to analyze the acquired aversion. On the following day, the preference for saccharin was evaluated by a two-bottle choice test (one bottle containing water along with another with saccharin). This preference was estimated as the consumption of saccharin versus the total consumption, i.e., the ratio between the saccharin consumption/saccharin consumption + water consumption (100 ×). Because of this ratio, percentages of 50% indicate equal consumptions of water and saccharin. Percentages of 0% indicate no consumption of saccharin, and 100% indicate no water consumption. Fig. 1 shows the behavioral procedure.

Histology

When the experiment was completed, the animals received a lethal overdose of sodium pentobarbital and were transcardially perfused. Following that, the brains were extracted and stored in 10% formalin solution and subsequently cryo-sectioned (Erma-422 cryostat, Tokyo) at approximately 45 µm. The slides were stained with cresyl violet and were examined using an optical microscope (CH-30, Olympus). Images of the slides were captured with an Olympus TV camera (U-PMTVC; 7M 03796, Japan).

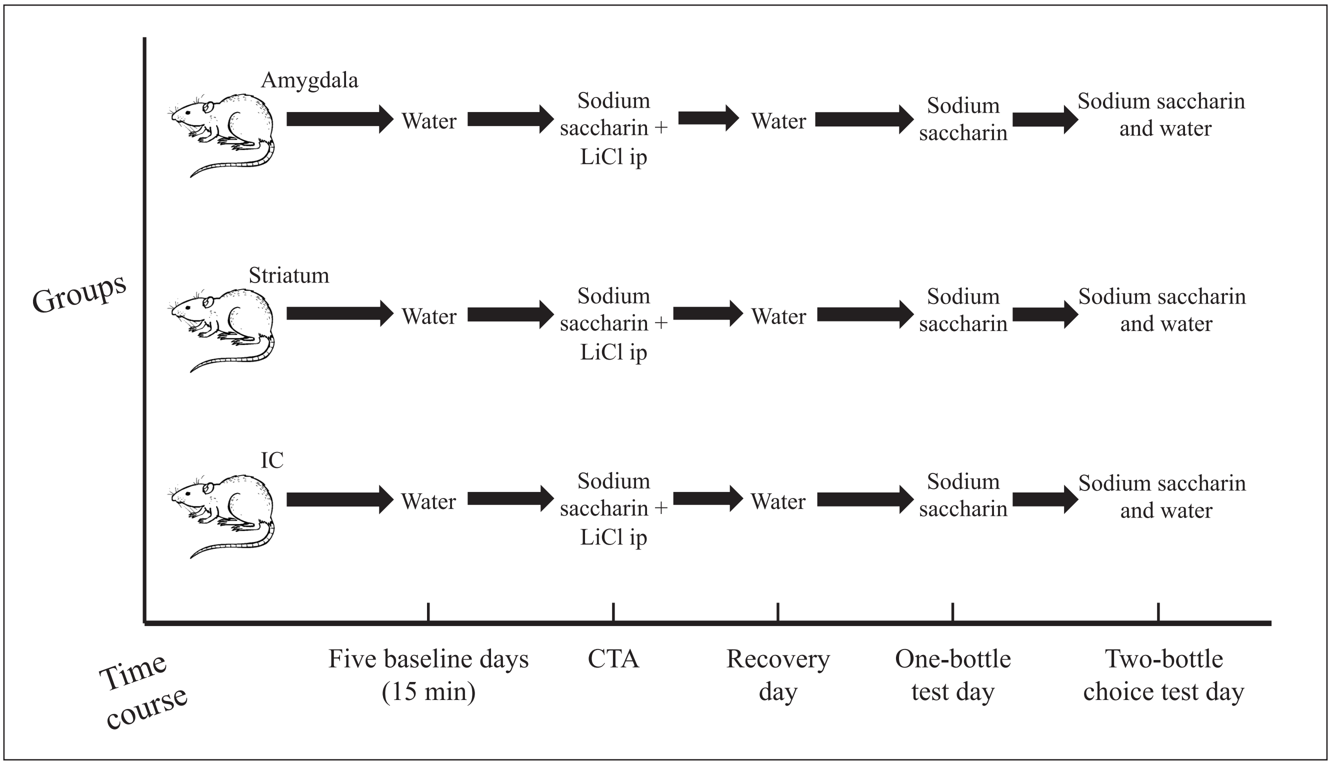

Fig. 1. Behavioral procedure. CTA, conditioning day; Amygdala, group with amygdaloid lesions; Striatum, group with striatal lesions; IC, intact control group. LiCl ip, lithium chloride intraperitoneal.

Statistical analysis

The effects of the lesions on the acquisition of CTA were analyzed using a 3×3 factorial design, with one between-group factor (lesion) with three levels (amygdaloid lesions, striatal lesions, and IC animals without lesions) and one inter-group factor (day) with three levels (baseline, conditioning, and one-bottle test days). The data from the baseline, conditioning, and one-bottle test sessions were analyzed with a factorial analysis of variance (ANOVA), and the significant factors were analyzed using one-way ANOVAs. For the significant factors and interactions, Newman-Keuls post-hoc tests were applied to analyze the differences. The consumption on the one-bottle test day was analyzed with a between-group (lesion) factorial covariance analysis (ANCOVA), with the consumption on the conditioning day as covariate. The preference for saccharin in the two-bottle choice test was calculated based on the consumption of saccharin relative to the total consumption, and the resulting percentage was analyzed with a between-group (lesion) factorial ANOVA. In all the tests, the critical level of significance for differences was set to $P<0.05$.

RESULTS

Histological analysis

The electrolytic lesions induced extensive bilateral damage in the groups with lesion in the amygdala and

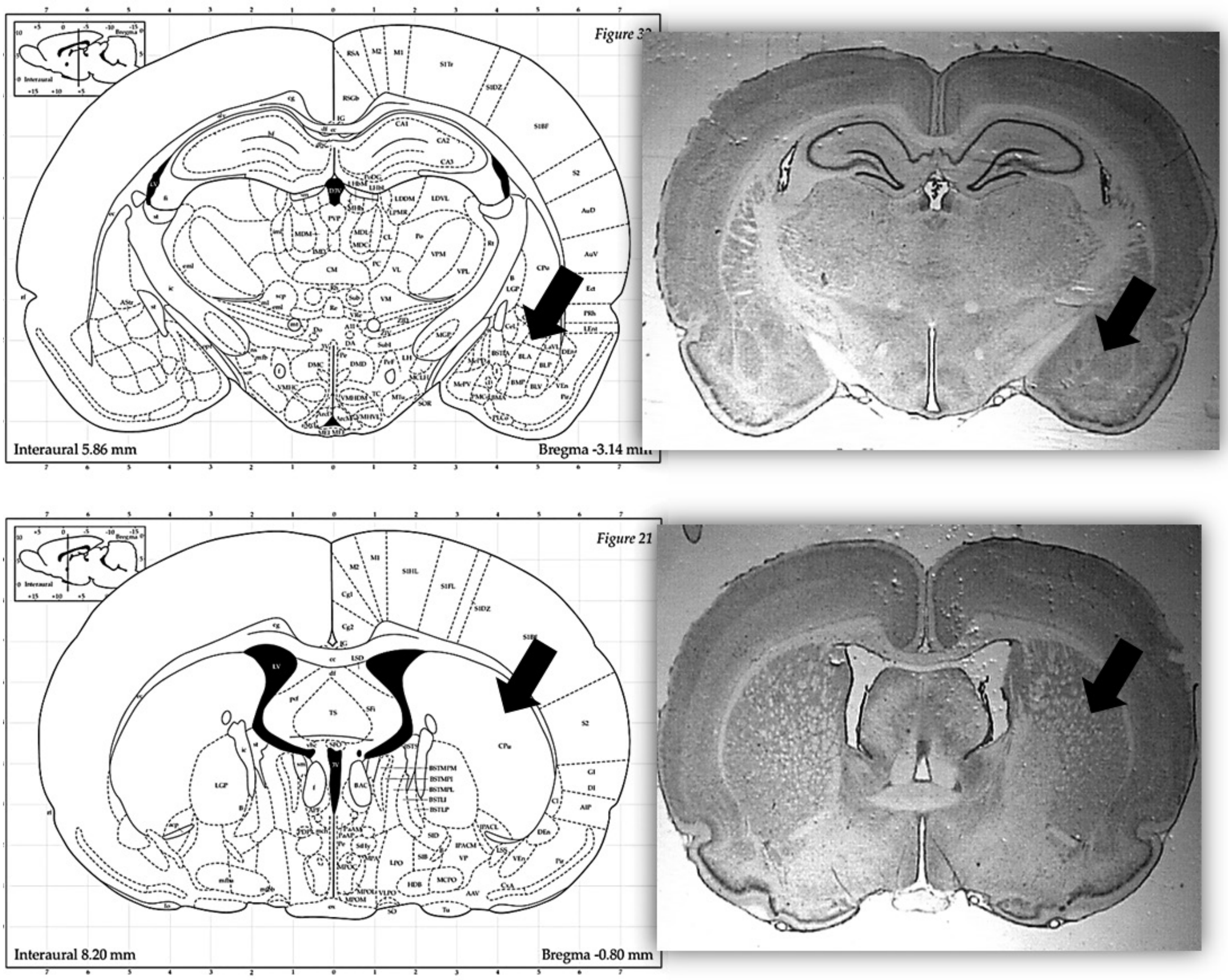

Fig. 2. Coronal brain sections from rats without lesions (IC, intact control animals). The arrows in the upper sections indicate the intact amygdala (on the right) and the anatomical localization of the amygdala in a neuroanatomical atlas (on the left). The arrows in the lower sections indicate the intact striatum (on the right) and the anatomical localization of the striatum in a neuroanatomical atlas (on the left) (Paxinos and Watson 1982, with permission from authors).

the striatum. In all animals with amygdaloid lesions, the electrolytic lesions induced damage in the basolateral, lateral, basomedial, and central nuclei. In one animal, the amygdaloid lesions tended to extend ventrally to adjacent areas (with no cortical damage), and dorsally reached the border region of the putamen. The striatal lesions induced damage in the dorsal part of the striatum in all animals. The maximum extension of lesions reached the ventral part of the striatum and the internal capsule, as well as a minimal part of the neocortex and the external capsule. The most dorsomedial lesions of the striatum reached the lateral part of the lateral ventricles. Fig. 2 shows representative coronal brain sections from intact control (IC) animals without lesions in the amygdala and striatum. Figs 3 and 4 show representative coronal brain sections from animals with lesions in the amygdala and striatum, respectively, and diagrammatic reconstructions of the maximum and minimum extensions of these lesions.

Behavioral results

At the end of the seven day postoperative recovery period, all animals showed a consumption pattern similar to that of the baseline period, with no apparent intense changes in body weight in any group.

One-bottle test

The one-bottle test showed that the magnitude of taste aversion was significantly reduced in the group with amygdaloid lesions when compared with the group of no-lesion animals. On the conditioning day, no neophobia was found in the group with amygdaloid lesions when compared with the striatal lesion and without lesion groups. Fig. 5 illustrates the mean consumption of each group on the baseline, conditioning, and one-bottle test days.

An ANOVA of the mean consumptions on the baseline, conditioning, and one-bottle test days indicated a signif-

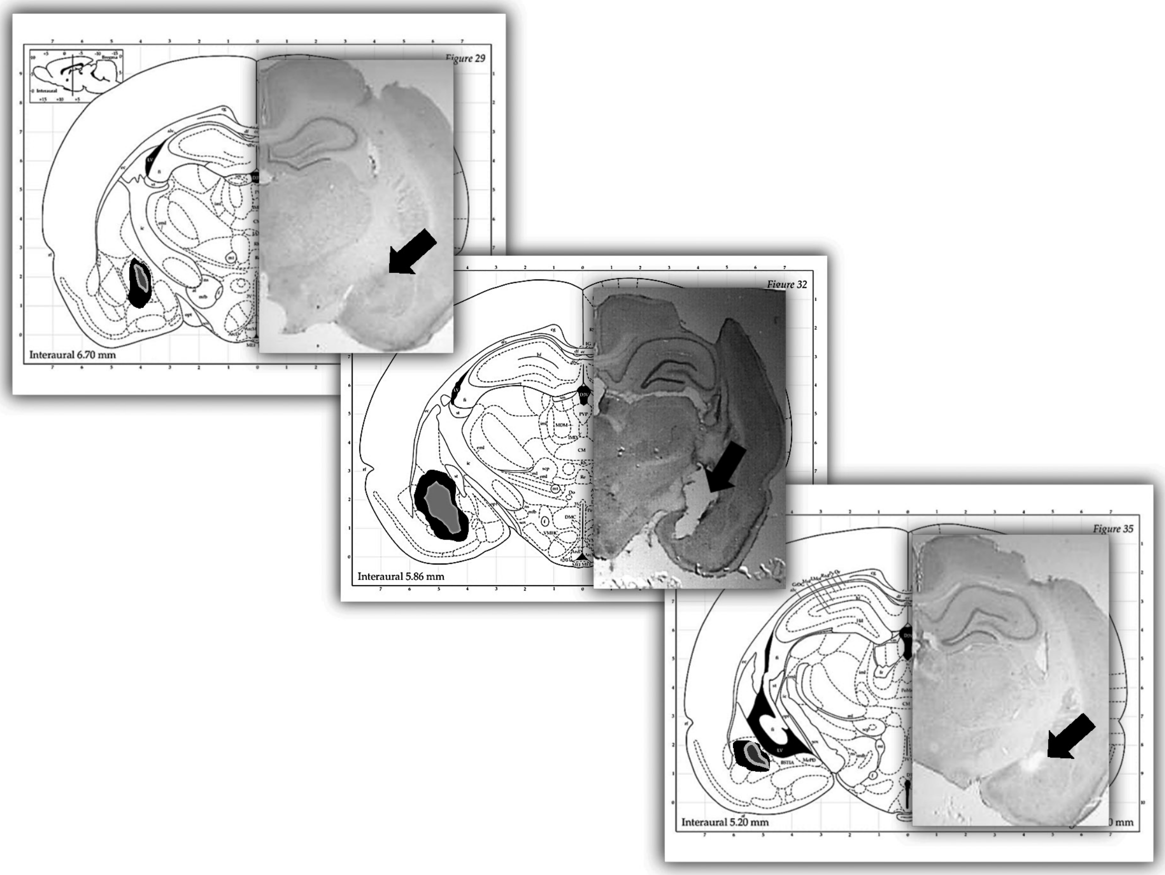

Fig. 3. Coronal brain sections from rats with lesions of the amygdala. The three overlapping images represent the minimum and maximum extension of the amygdaloid lesions, indicated by gray and black marks respectively, along the anterior-posterior axis. The arrows on the right indicate the localization of the amygdaloid lesions along the anterior-posterior axis (Paxinos and Watson 1982, with permission from authors).

icant effect of day ($F_{2,38}$=11.45, P<0.01) and an interaction between lesion and day ($F_{4,38}$=5.23, P=0.01). No significant effect was found for the lesion factor ($F_{2,19}$=2.75, P=0.09). A unifactorial ANOVA of the values for the day factor revealed a significant effect ($F_{2,42}$=6.96, P=0.01). Newman-Keuls tests indicated that mean consumption on the baseline day was higher than consumption on the one-bottle test day (P=0.01). Additionally, consumption on the conditioning day was greater than on the one-bottle test day (P=0.01). A unifactorial ANOVA of the interaction indicated a significant effect of lesion factor on the conditioning day ($F_{2,19}$=8.42, P<0.01); consumption in the group with amygdaloid lesions was higher than in the striatal lesions (P<0.01) and without lesions (P<0.01) groups. A unifactorial ANOVA of the consumptions in the one-bottle test revealed a significant effect of the lesion factor ($F_{2,19}$=4.79, P=0.02); mean consumption of saccharin in the amygdaloid lesions group was higher than in the without lesions group (P=0.01). No other significant differences were found.

A repeated-measures ANOVA conducted to analyze the consumptions throughout the baseline, conditioning, and test days indicated that mean consumption in the without lesions group differed across days ($F_{2,10}$=20.01, P=0.01). Newman-Keuls tests indicated that the mean consumption on the baseline day was greater than on the conditioning (P=0.02) and one-bottle test (P=0.01) days, and that mean consumption on the conditioning day was greater than on the one-bottle test day (P=0.01). The mean consumption of the group with lesions of the amygdala also differed across days ($F_{2,14}$=12.72, P=0.01). Newman-Keuls tests revealed that mean consumption on the conditioning day was greater than on the baseline (P=0.01) and one-bottle test (P=0.01) days. No significant differences across days were found in the group with lesions of the striatum ($F_{2,14}$=1.06, P=0.37).

An ANCOVA of the mean consumptions of saccharin on the one-bottle test day in relation to the consumptions on the conditioning day (as covariate variable) revealed a significant effect of the lesion factor ($F_{2,27}$=5.3,

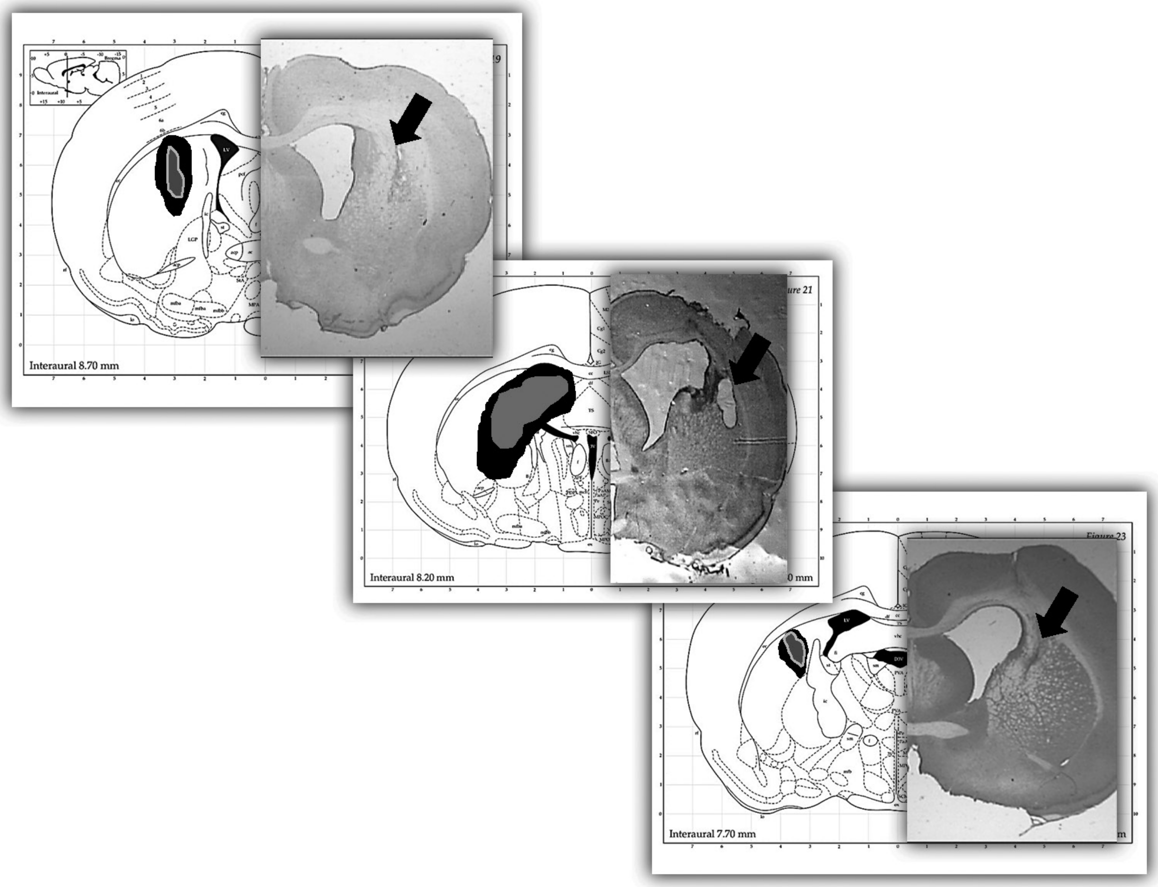

Fig. 4. Coronal brain sections from rats with lesions of the striatum. The three overlapping images represent the minimum and maximum extension of the striatal lesions, indicated by gray and black marks respectively, along the anterior-posterior axis. The arrows on the right indicate the localization of the striatal lesions along the anterior-posterior axis (Paxinos and Watson 1982, with permission from authors).

P=0.03). The mean consumption of the amygdaloid lesions group was greater than that of the without lesions group ($F_{1,18}$=5.9, P=0.02). No significant differences were observed between the consumptions of the groups with amygdaloid and striatal lesions ($F_{1,18}$=8.1, P=0.25) or between the consumptions of the striatal lesions and without lesions groups ($F_{1,18}$=7.3, P=0.1).

Two-bottle choice test

Preference for saccharin (i.e., the consumption of saccharin relative to the total consumption in the two-bottle choice test) is a measure that is able to detect small taste aversions because, unlike the one-bottle test, animals can choose between water and the conditioned stimulus. A percentage of 100% indicates that no taste aversion was acquired. The results of the analysis of differences between groups in the percentages of preference for saccharin were consistent with the results observed in the one-bottle test, although a marginal but non-significant effect of the lesion factor was found in the ANOVA of the percentages ($F_{2,19}$=2.7, P=0.09). Newman-Keuls tests indicated that there were no significant differences between groups for percentages, but a marginally greater preference for saccharin was revealed in the group with amygdaloid lesions (P=0.06). Thus, when the two-bottle choice test followed the one-bottle test, a modulation of the magnitude of taste aversion induced by amygdaloid lesions was also observed, although the differences in this second test did not reach significance. Fig. 6 shows the percentage of preference for saccharin for each group.

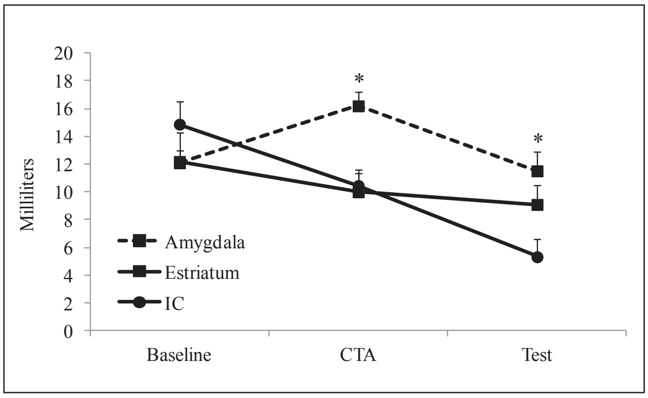

Fig. 5. Mean water and saccharin (conditioned stimulus) consumptions by the groups (in milliliters) during different stages of the behavioral procedure and standard deviations. IC, intact (without lesions) control animals; Baseline, fith day of water consumption; CTA, conditioning day. One-bottle test was used to analyze the acquired taste aversion. For brevity, the water consumption after conditioning is not represented. The saccharin consumption of the group with lesions of the amygdala on the conditioning day was greater than those of the striatal lesions (P<0.01) and without lesions (P<0.01) groups. An ANCOVA of the mean consumptions of saccharin on the one-bottle test day with respect to the consumptions on the conditioning day indicated that the mean consumption of the amygdaloid lesions group was greater than that of the without lesions group ($F_{1,18}$=5.9, P=0.02). Significant values are represented by asterisks. These results suggest that amygdaloid lesions affect the novelty perception of the taste stimulus and thus reduce the magnitude of the acquired taste aversion.

DISCUSSION

The results of the one-bottle test indicated that amygdaloid lesions significantly reduced the magnitude of acquired taste aversion when compared to animals without lesions and considering the consumptions on the conditioning day. The two-bottle choice test showed a greater preference for saccharin, marginal but not significant, in the group with lesions of the amygdala. It is assumed that the choice test is sensitive to detect weak taste aversions, although it has also been proposed that this method of evaluation may obscure between-group differences in aversion strength (Batsell and Best 1993). In the present study, the non-significant differences found in the choice test may be due to the fact that the animals were previously exposed to the conditioned stimulus on the one-bottle test day, and therefore the two-bottle choice test day was actually an extinction day, which may have minimized the differences between groups. The percentage of preference for saccharin derived from the choice test was higher than 50% only in the group with amygdaloid lesions, which is congruent with the results of the one-bottle test, and shows that

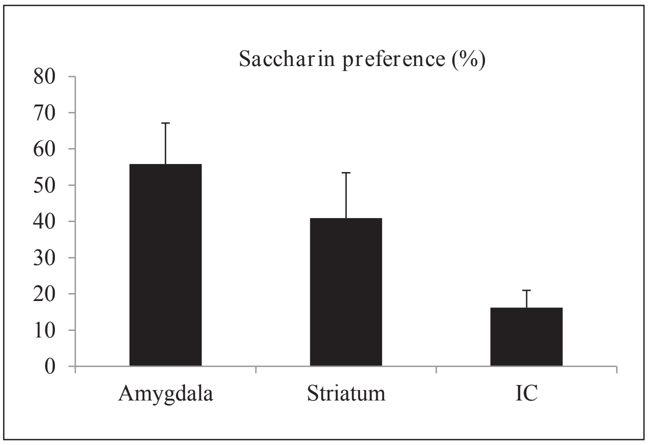

Fig. 6. Percentage of preference for saccharin solution of each group (obtained from the consumptions recorded in the two-bottle choice test) and standard deviations. IC, intact (without lesions) control animals. The percentage of preference for saccharin was calculated as the ratio between the saccharin consumption/saccharin consumption + water consumption (100 ×). No significant differences were found between groups in the ANOVA of the percentages ($F_{2,19}$=2.7, P=0.09), but a marginally greater preference for saccharin was revealed in the group with amygdaloid lesions (P=0.06), which is consistent with the results obtained using the one-bottle test.

the magnitude of taste aversion in the animals with lesions of the amygdala was clearly lower than in the other groups. The results of this second test may also have been influenced by the fact that the two-bottle choice test was a novel drinking situation for all animals, which could have resulted in some kind of bottle/place preference during choice. However, no 0% or 100% percentages (which would indicate no consumption of saccharin or water, respectively) were found in this test. In addition to the effects of lesions on CTA, animals with amygdaloid lesions showed no evidence of neophobic response to saccharin on the day of conditioning when compared to animals without lesions. Animals with lesions of the dorsal striatum did not significantly reduce consumption on the day of conditioning in relation to the baseline (perhaps as a non-specific effect due to the size of the lesion), but their consumption of saccharin on the conditioning day was significantly lower than that of the animals with amygdaloid lesions. Moreover, animals with amygdaloid lesions did increase consumption on the conditioning day in relation to the baseline. With respect to these results, it can be argued that the severe water deprivation of the procedure could have affected the motivation to consume fluid, and consequently, the estimation of the magnitude of taste aversion is limited. However, this water deprivation is used in the CTA paradigm (Bures 1998, Bernstein 1999) because it induces a similar physiological state in all animals, compared to a non-restrictive deprivation. This facilitates the discrimination of the effect between the different groups or interventions, although the precise magnitude of the aversion in all groups is influenced by the water restriction. CTA procedures with similar water restriction have also resulted in significant effects of the respective interventions (Bernstein and Koh 2007, Ferreira et al. 2006, López-Velázquez et al. 2007).

The electrolytic lesion of the basolateral amygdala has also induced a reduced aversion in previous studies (Reilly and Bornovalova, 2005). The electrolytic lesion is a non-selective method to induce lesion. This procedure induces damage to target cells and fibers of passage. For this reason, the effect of electrolytic lesions of the amygdala was also attributed to effects on critical connections for the acquisition of CTA (Dunn and Everitt 1988, Fitzgerald and Burton 1981, Schafe and Bernstein 1996, Spray and Bernstein 2004). However, it has been shown that excitotoxic lesions of the basolateral amygdaloid complex severely compromise CTA without affecting the parabrachial-insular pathway (Morris et al. 1999). Therefore, the findings of the present study are consistent with the evidence supporting the involvement of the amygdala in CTA (Schafe and Bernstein 1996, Yamamoto 1993). However, considering the extent of the lesions in the present study, it can be concluded that the amygdala does not seem to be a critical structure for the acquisition of this conditioning. Rather, the results point to a modulating function of the amygdala on the acquisition of CTA. A reduced taste aversion has also been reported with selective lesions of the basolateral amygdala (Molero-Chamizo 2017) and with more extensive lesions affecting the lateral nuclear group (St. Andre and Reilly 2007, Yamamoto et al. 1995), but not with lesions of the central nucleus (Agüera and Puerto 2015, Morris et al. 1999, Reilly and Bornovalova 2005, St. Andre and Reilly 2007). Moreover, in a recent study, excitotoxic lesions of each of the three main nuclei of the amygdala revealed that the acquisition of CTA is reduced only after selective lesions of the basolateral nucleus of the amygdala (Molero-Chamizo and Rivera-Urbina 2017). Lesions of the central and medial nuclei of the amygdala did not affect the acquisition of CTA. Thus, the basolateral amygdala seems to be the specific amygdaloid nucleus involved in the acquisition of taste aversion. All these findings are congruent with the results obtained in the present study. It can therefore be argued that the effects on CTA observed with amygdaloid lesions might be related to the specific damage induced on the basolateral amygdala. In the current study the lesions of the amygdala affected the response to the taste stimulus on the conditioning day (the consumptions of the group with amygdaloid lesions were increased on the conditioning day when compared to baseline and to the other groups), and the mechanism by which the amygdala intervenes to modulate the magnitude of taste aversions may depend on the perception of novelty phenomena attributed to the amygdala, and particularly, to the basolateral amygdala (Reilly and Bornovalova 2005, St. Andre and Reilly 2007, Reilly 2009). Similar effects on CTA and taste neophobia have been described with lesions of the basolateral amygdala (Kesner et al. 1992), which also support the idea that the amygdaloid mechanism involved in the acquisition of CTA is dependent on the activity of the basolateral amygdala and its function in the perception of taste novelty. As a result, lesions of the basolateral amygdala (as well as more extensive lesions of the amygdala) can reduce the processing of taste novelty and, therefore, may attenuate the magnitude of CTA.

CONCLUSIONS

Extensive lesions of the amygdala do not prevent the acquisition of CTA but reduce the magnitude of the acquired aversion. Similar effects have been described with selective lesions of the basolateral amygdala, which possibly suggest that the effects on CTA reported with lesions of the amygdala may be due to the damage induced in the basolateral nucleus of the amygdala or the lateral nuclear group. Moreover, in this study the extensive lesions of the amygdala also affected the perception of taste novelty. Therefore, it can be concluded that the reduced taste aversion detected after extensive lesions of the amygdala was a consequence of the interruption of neophobia on the conditioning day, a phenomenon that also seems to depend on the activity of the basolateral amygdala. Future studies, beyond lesions studies, may also shed light on the role of the amygdala and its nuclei in the acquisition of CTA.

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