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Effect of Amygdaloid Lesions on Ethanol Intake in Rats

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KOLAKOWSKA, L., C. LARUE-ACHAGIOTIS AND J. LE MAGNEN. *Effect of amygdaloid lesions on ethanol intake in rats.* PHARMAC BIOCHEM BEHAV **23**(3) 333–338, 1985.—The effect of electrolytic lesions of the amygdala on ethanol intake in ethanol naïve rats has been studied. Rats with basolateral nuclei and lateral nuclei lesions showed a reduced neophobic response to an ethanol solution. However, the ethanol intake was too small in normal and lesioned rats to augment aversion through conditioning. Oral intake of ethanol supplemented by intraperitoneal ethanol injection to reach 2 g/kg indeed enhanced the initial sensory aversion to ethanol. This induced aversion was attenuated after basolateral lesions. An initial aversion to a mixed ethanol-sucrose solution was abolished after basolateral lesions, while the lateral lesions induced an initial preference for this solution. The initial oral intake of ethanol-sucrose in normal rats was again too small to induce the conditioned taste aversion (C.T.A.). Despite the high oral intake of this solution, rats with basolateral lesions did not show a conditioned aversion while laterally lesioned rats exhibited a strong conditioned aversion to the ethanol-sucrose mixture. The results which confirm the suppression of the C.T.A. by basolateral amygdala lesions are discussed in relation to the role of toxicophobia in ethanol intake by rats.

Basolateral and lateral amygdala Ethanol intake Neophobia C.T.A.

EXPERIMENTAL data suggest that the spontaneous low intake of ethyl-alcohol solutions by rats is due to two complementary mechanisms. In a choice situation between a low concentration ethanol solution and water, an unlearned sensory aversion analogous to that exhibited toward a bitter solution limits intake to 1–2 g/kg of body weight. Olfactory bulbectomy modifies the response [10–20]. Sweetening the solution enhances intake without delay [13, 14, 17]. In individual rats the ethanol aversion is correlated to the aversive threshold toward a bitter quinine solution [16]. This sensory aversion is not reversed but overcome in a single bottle ad lib presentation of the ethanol solution as the only source of fluid. Ethanol intake is also augmented by food deprivation or restriction [22–25]. However, in these conditions of forced intake, it was shown that the daily intake does not exceed 6 to 7 g/kg [23]. This limit corresponds to the daily oxidative capacity of ethanol by rats, determined to be 300 mg/hr/kg. This limit of the rate of intake at the level of the rate of elimination of ethanol from the body has been explained by the occurrence of an ethanol induced taste aversion [15–18]. When ethanol consumption comes to exceed its elimination from the blood, the blood ethanol level, through its acute toxic activity on the central nervous system (C.N.S.) acts as an unconditioned stimulus (U.C.S.) to reinforce the sensory aversion. This has been directly demonstrated. The intraperitoneal (IP) injection of ethanol (1.5–2.0 g/kg) like that of toxic LiCl salt following the free intake of a saccharin solution induces aversion to the solution [2,5].

In rats this ethanol induced aversion to saccharin is individually correlated to the nervous sensitivity to ethanol, as tested by motor impairment or hypothermia under ethanol [24].

In a previous work, we have shown that lesions of the basolateral nuclei of the amygdala in rats abolished the neophobic response to a shortly presented saccharine solution and suppressed the LiCl induced aversion [12]. In the present work, we have studied the conditioning of an enhanced aversion to an ethanol solution, through its post-ingestive toxic activity in normal and amygdala lesioned rats. It was anticipated that the disruption of the toxicophobic conditioning by the basolateral nuclei lesion would lead to a sustained high level of acceptance of an ethanol solution by rats.

METHOD

Animals

Male Wistar rats weighing 250–300 g at the beginning of the experiment were used. They were individually housed. Food and water were available ad lib prior to surgery. A 12 hr light-dark cycle was monitored (light 7 a.m.–7 p.m.).

Surgery Procedure

Surgery was performed under pentobarbital anesthesia. Bilateral electrolytic lesions were aimed stereotaxically in the basolateral or lateral nuclei of the amygdala using the

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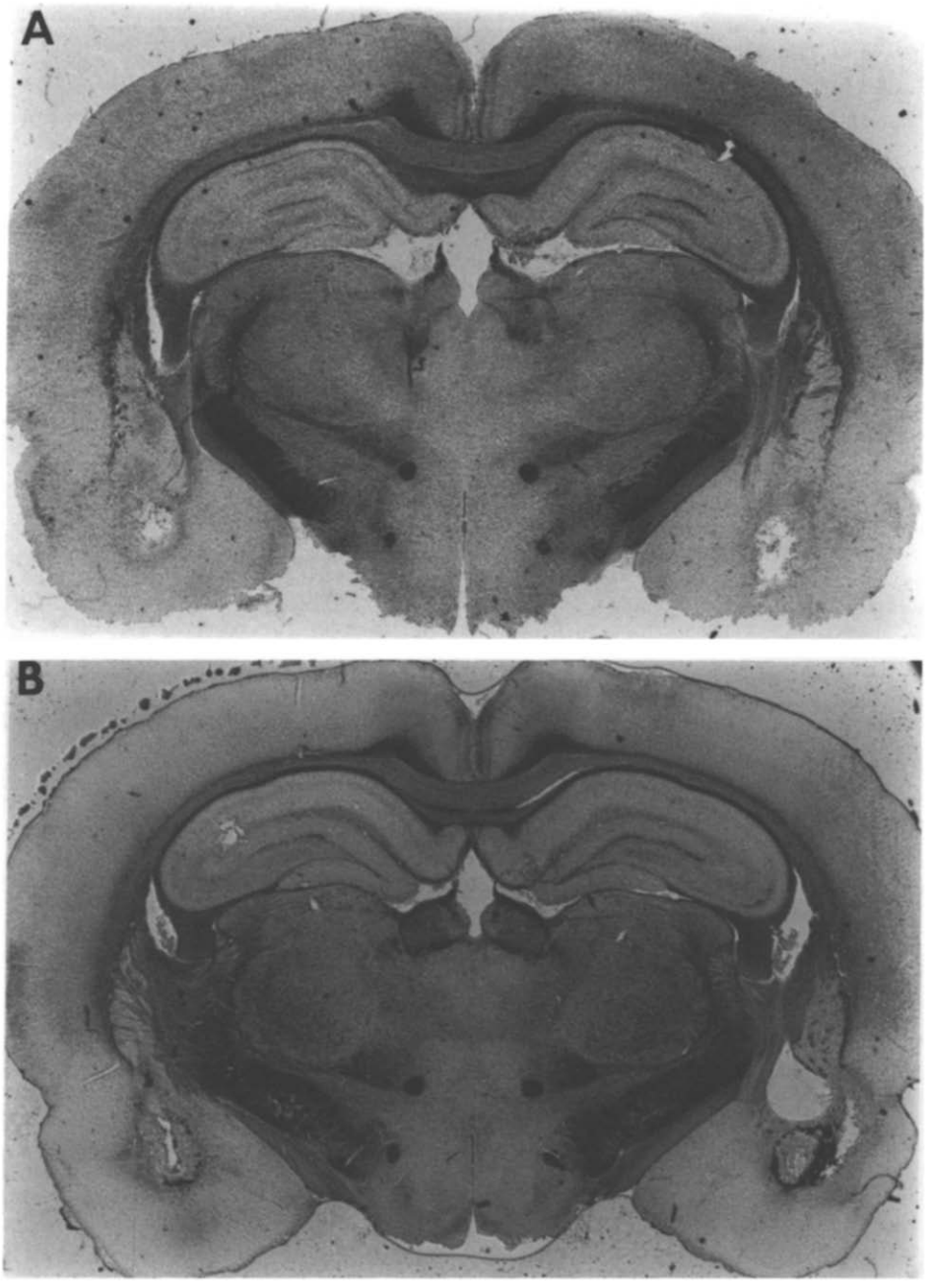

FIG. 1. Examples of the amygdala lesions from Group ABL (A) and Group AL (B).

following coordinates [4]: for the basolateral nucleus (AB): AP=4.6 mm anterior to the ear bar; L=5 mm lateral to the sagittal sinus; H=7.35 below the cortical surface; for the lateral nucleus (AL): AP=5.4 mm; L=5.3 mm; H=6.75 mm. Stainless steel electrodes were used. They were isolated except for 0.3 mm at the tip.

Lesions were made by passing a direct anodal current of 2 mA for 30 sec for ABL and 20 sec for AL. The indifferent electrode was attached to the tail.

Histology

At the end of the experiment animals were anesthetized with pentobarbital and perfused with physiological saline followed by 10% Formalin. The brains were removed and stored in 10% Formalin for 48 hours and were then cut into 40 micron coronal sections (on a freezing stage microtome). The sections were stained with blue toluidine. Size and localization of lesions were examined by light microscopy.

This histological examination revealed that 26 of the 30 animals in Group ABL, and 24 of 27 in Group AL were effectively lesioned in the basolateral or lateral nuclei of the amygdala respectively. Figure 1 illustrates the well circumscribed lesions in the 2 groups; no overlap exists in these selected rats between the 2 types of lesion.

TABLE 1

PURE ALCOHOL INTAKE (g/kg) IN ETHANOL INJECTED (N_E, ABL_E, AL_E) AND NONINJECTED RATS (N, ABL, AL)

	Rats conditioned by oral intake of ethanol				Rats conditioned by oral intake of ethanol + ethanol injection			
Day	N	ABL	AL		N_E	ABL_E	AL_E	
6	0.89 ±0.05	0.97 ±0.09	0.99 ±0.15	H=1.12 n.s.	0.86 ±0.04	0.85 ±0.07	1.00 ±0.08	H=1.46 n.s.
9	1.70 ±0.3	0.96 ±0.09	1.48 ±0.3	H=5.28 n.s.	0.19 ±0.06	0.50 ±0.09	0.68 ±0.1	H=7.71 $p<0.05$

General Experimental Procedure

After surgery rats were given free access to food and water for 5–6 days. Then lesioned and normal animals were placed on a daily schedule of water drinking. They were offered a graded drinking tube from 9 to 9.30 a.m. and from 4.00 to 6.00 p.m. No food was available during the morning session. Baseline water intake during the morning sessions was measured for 5 consecutive days.

On Day 6, conditioning day, rats were offered a novel ethanol or ethanol-sucrose solution instead of water during the 30 min morning presentation.

On Days 7 and 8, all rats received water in the morning session.

On Day 9, test day, rats were offered the solution they had been given on Day 6.

From Day 10 to Day 18, rats were maintained on the same solution as on Day 6 and 9.

EXPERIMENT 1

The effects of amygdala lesions upon the oral intake of an ethyl-alcohol solution were studied in the first experiment.

Twenty-five rats were used and ascribed to 1 of 3 groups, namely, normal (N, n=8), basolateral (ABL, n=9) and lateral (AL, n=8). On Day 6, rats were offered an ethanol solution (8% w/v) to drink during the morning session. The test procedure from Days 7 to 18 was the same as indicated above.

RESULTS

Water intake for the 5 consecutive days of control was significantly lower in both lesioned groups compared to unoperated animals ($F(2,22)=11.42$, $p<0.01$; Dunnett test: ABL/N: $t=4.15$, $p<0.01$; AL/N: $t=4.16$, $p<0.01$).

In the 3 groups, rats receiving ethanol for the first time showed a sharp decrease in consumption of fluid as compared to their own water baseline (N: $t=16.07$, $p<0.01$; ABL: $t=8.78$, $p<0.01$; AL: $t=6.84$, $p<0.01$; Fig. 2). In N, ABL and AL groups, the reduction in intake was 8.1±0.5 ml, 4.8±0.5 ml and 5.2±0.7 ml respectively. The reductions in ABL and AL groups were both significantly lower than in normal rats ($F(2,22)=8.67$, $p<0.01$; Dunnett test: N/ABL: $t=3.86$, $p<0.01$; N/AL: $t=3.32$, $p<0.01$). Proportionally to their lower previous water intake, these reductions are also lower than in unoperated controls so that alcohol intake becomes not significantly different in the 3 groups, $F(2,22)=0.22$, n.s.

On Day 9, ethanol consumption increased in Groups N and AL (N: $t=2.3$, $p=0.05$; AL: $t=2.63$, $0.01<p<0.05$) while it did not in Group ABL ($t=0.37$, n.s.; Fig. 2). However, these changes were not significantly different in these 3 groups, $F(2,22)=3.29$, n.s.

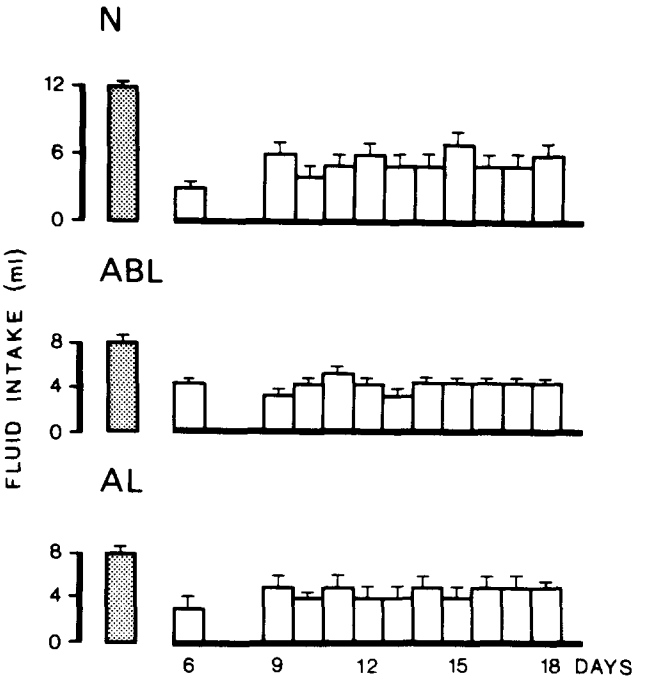

FIG. 2. Ethanol intake (mean±SEM) on conditioning day (Day 6), test day (Day 9) and consecutive days (10–18) compared to water baseline (shaded bars) in normal (N), basolateral lesioned (ABL) and lateral lesioned (AL) rats.

Pure alcohol intake (g/kg of body weight) on conditioning and test days for these 3 groups is represented in the Table 1.

Oral intake of alcohol was unchanged for 9 consecutive days (from Days 10 to 18) in normal and lesioned animals (Fig. 2). Normal rats drank slightly more ethanol than lesioned rats.

EXPERIMENT 2

The results of the preceding experiment indicated that the initial oral intake of 0.89 g/kg, 0.97 g/kg and 0.99 g/kg of pure

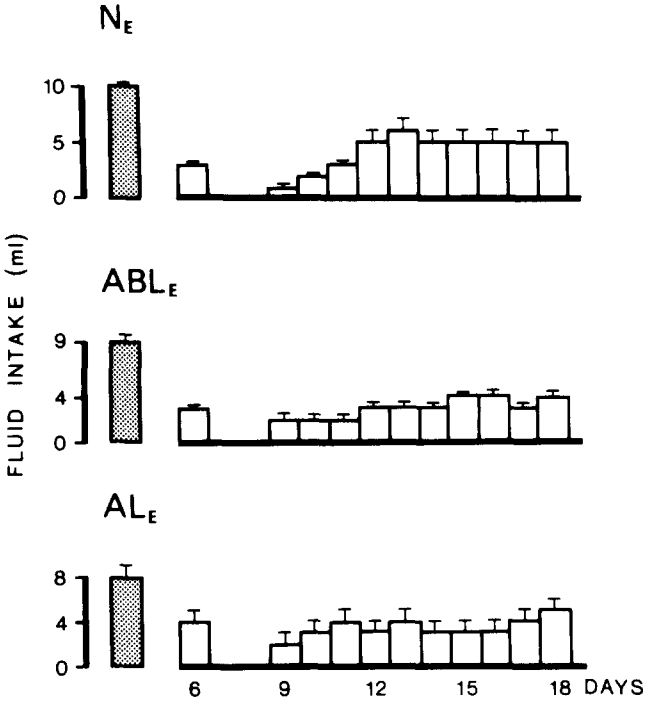

FIG. 3. Ethanol intake (mean±SEM) on conditioning day (Day 6), test day (Day 9) and consecutive days (10–18) compared to water baseline (shaded bars) in ethanol injected normal (N_E), basolateral lesioned (ABL_E) and lateral lesioned (AL_E) rats.

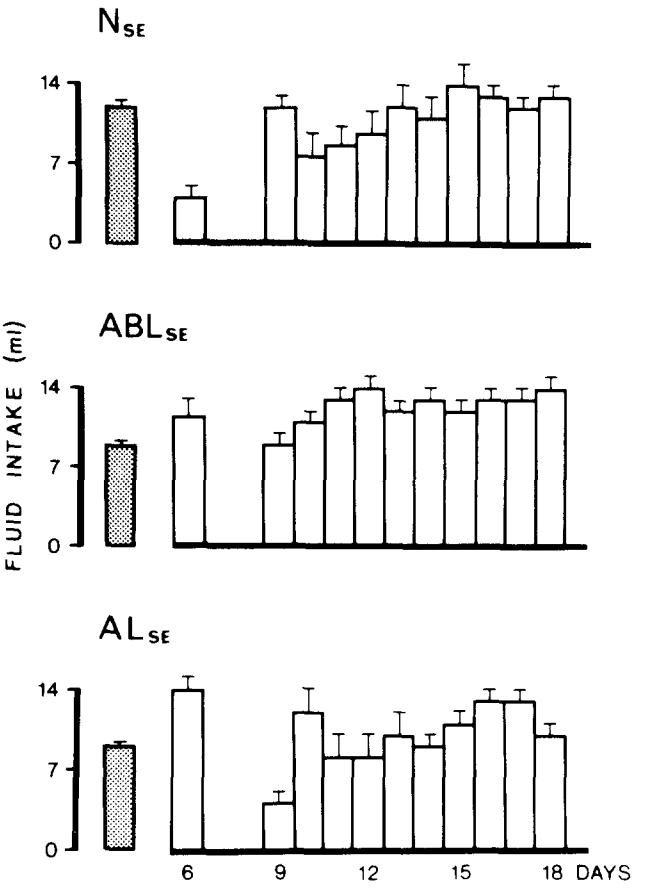

FIG. 4. Ethanol-sucrose intake (mean±SEM) on conditioning day (Day 6), test day (Day 9) and consecutive days (10–18) compared to water baseline (shaded bars) in normal (N_E), basolateral lesioned (ABL_E) and lateral lesioned (AL_E) rats.

alcohol in N, ABL and AL groups respectively was not sufficient to reinforce aversion to ethanol through the postingestive effect. In the second experiment we have attempted to establish a conditioned taste aversion to an ethanol solution by increasing the postingestive effects through pairing oral intake and IP injection of ethanol.

Twenty-four rats were used (normal: N_E, n=8, basolateral: ABL_E, n=9; lateral: AL_E, n=7). Food and water conditions were identical to those of Experiment 1. After 5 days of water presentation (water baseline), rats were offered an ethanol solution (8% w/v) to drink on Day 6. Oral intake was followed by an IP administration of an ethanol solution (10% w/v). The dose injected was adjusted to the preceding oral intake so as to achieve a total dose of ethanol of 2 g/kg (oral intake plus IP injection). The test procedure from Days 7 to 18 was the same as indicated above.

RESULTS

Like in Experiment 1, the 3 groups showed a significant decrease in consumption of the ethanol solution on Day 6 as compared with water baseline (N_E: $t=16.92$, $p<0.01$; ABL_E: $t=9.69$, $p<0.01$; AL_E: $t=14.67$, $p<0.01$; Fig. 3). Again we observed a lower water baseline in lesioned rats ($F(2,21)=3.99$, $0.01<p<0.05$; Dunnett test: ABL_E/N_E: $t=2.49$, $0.01<p<0.05$; AL_E/N_E: $t=2.39$, $0.01<p<0.05$). However, the relative reductions of alcohol intake in ABL_E (5.3±0.5 ml) and AL_E (4.8±0.3 ml) groups as in Experiment 1 were less than that of group N_E (7.1±0.4 ml; $F(2,21)=6.42$, $p<0.01$; Dunnett test: N_E/ABL_E: $t=2.75$, $0.01<p<0.05$; N_E/AL_E: $t=3.36$, $p<0.01$).

The oral intake supplemented by IP ethanol led to a significant reduction in intake on test day in the 3 groups (N_E: $t=11.83$, $p<0.01$; ABL_E: $t=2.37$, $p<0.05$; AL: $t=3.29$, $0.01<p<0.05$; Fig. 3). The decrease was 2.5±0.2 ml; 1.1±0.4 ml; and 1.8±0.5 ml in groups N_E, ABL_E and AL_E respectively. The decrease in ABL_E rats was significantly less than in N_E rats ($F(2,21)=3.76$, $0.01<p<0.05$; Dunnett test: $t=2.73$, $0.01<p<0.05$). Groups N_E and AL_E were not significantly different, $t=1.4$, n.s. The intake of pure alcohol on conditioning and test days for these 3 groups (N_E, ABL_E, AL_E) is represented in Table 1. In this table, it is shown that the amounts of pure ethanol drank by lesioned rats on Day 9 was significantly higher than in unoperated animals (ABL_E/N_E: $U=12.5$, $0.01<p<0.05$; AL_E/N_E: $U=7.0$, $0.01<p<0.05$).

Normal rats (N_E) increased their consumption from days 10 to 13. Like in nonsupplemented animals, the consumption of alcohol in Group N_E was slightly higher than in ABL_E and AL_E groups.

EXPERIMENT 3

It has been shown that the lesion of the amygdala attenuates neophobia to sweet solutions in rats [1, 15, 24]. This suggests that intake of a sucrose-ethanol mixture would be enhanced in amygdala lesioned rats. The postingestive toxic effect of this enhanced voluntary intake might introduce a conditioned taste aversion to the ethanol-sucrose solution.

Twenty-four rats were used (normal, N_{SE}, n=7; basolateral, ABL_{SE}, n=8; lateral, AL_{SE}, n=9). On Day 6, rats were offered an ethanol solution (8% w/v) mixed with sucrose (20% w/v). The test procedure from Days 7 to 18 was the same as indicated above.

RESULTS

Normal rats (N_{SE}) drank significantly less ethanol-sucrose solution than water ($t=9.8$, $p<0.01$, Fig. 4). After basolateral nuclei lesion (ABL_{SE}) rats drank slightly more ethanol-sucrose solution than water drank, $t=1.72$, n.s. In lateral rats (AL_{SE}), intake of the ethanol-sucrose solution was significantly higher than their own previous intake of water, $t=5.92$, $p<0.01$. The amount of pure alcohol drunk with this solution was 1.1±0.2 g/kg (0.5–1.8), 3.3±0.4 g/kg (2.0–5.5) and 4.1±0.3 g/kg (2.8–5.0) in N_{SE}, ABL_{SE} and AL_{SE} groups respectively.

During the second presentation of the ethanol-sucrose solution, normal rats (N_{SE}) showed a significant increase in consumption ($t=9.41$, $p<0.01$), which was not different from water-baseline ($t=0.24$, n.s., Fig. 4). The mean alcohol intake reached 3±0.3 g/kg (2.1–4.1) on Day 9. In ABL_{SE} rats, the ethanol-sucrose intake on Day 9 (9.4 ml) was slightly reduced as compared to Day 6 (11.6 ml; $t=1.23$, n.s.). Alcohol consumption was almost identical: it was 2.7±0.4 g/kg (0.9–4.2). Thus, neither normal nor ABL_{SE} rats displayed a conditioned taste aversion on test day.

By contrast in AL_{SE} rats, the preference for the ethanol-sucrose solution manifested on Day 6 disappeared on Day 9. On test day, AL_{SE} rats drank significantly less of an ethanol-sucrose solution than on conditioning day, $t=6.9$, $p<0.01$, and less than water baseline, $t=4.61$, $p<0.01$. Alcohol intake dropped from 4.1±0.3 g/kg (2.8–5.0) to 1.3±0.2 g/kg (0.6–3.0) on Day 9. Thus, AL_{SE} rats exhibited a strong conditioned taste aversion to the ethanol-sucrose solution.

From Days 10 to 18, the ethanol-sucrose consumption was not significantly different from day to day in N_{SE} group ($F(6,9)=2.52$, n.s., Fig. 4) and was not significantly different from water baseline. ABL_{SE} rats showed a little increase in ethanol-sucrose consumption from Days 10 to 12. From Days 11 to 18, their consumption of ethanol-sucrose was significantly higher than water-baseline (t values are respectively for each day: 3.22; 2.82; 3.58; 4.81; 2.30; 3.56; 3.75; 5.33, $p<0.05$). AL_{SE} rats showed a characteristic behavior during consecutive days of ethanol-sucrose presentation. Intake of this solution increased in all animals from Day 9 to Day 10. On Day 11, some rats showed a renewed conditioned aversion by decreasing their consumption of the ethanol-sucrose solution. The general tendency is an alternation between raise and reduction in ethanol-sucrose consumption.

DISCUSSION

In a previous work we have shown that lesioning the basolateral nuclei of the amygdala suppressed the neophobic response to a saccharin solution while lesions of the lateral nuclei of the same structure entirely abolished this response to novelty [12]. This is consistent with other studies [1, 3, 7, 9, 11, 21].

The results of Experiment 1 indicate that the initial ethanol intake relative to previous water intake of each group is larger in basolateral and lateral lesioned rats compared to intact controls. It is apparent despite the differences of water intake between lesioned and unlesioned rats. This difference also manifested in the two other experiments, indicating a tendency of basolateral and lateral lesions of amygdala to reduce the overall fluid intake. The relative higher intake of ethanol in lesioned rats could be tentatively interpreted as the effect of a suppression of the neophobic response identical to that observed with saccharin solution. However the maintained low intake of ethanol (relative to water) in the two groups of lesioned rats may be interpreted as the manifestation not of neophobia but rather of the spontaneous sensory aversion to an ethanol solution. This is consistent with published data showing that amygdaloid lesions do not alter a spontaneous sensory aversion such as the response to a quinine adulterated fluid [1].

Thus the initial response of intact rats to ethanol solution would comprise two components, the neophobic response added to the spontaneous and persistent aversion, the former only being altered by amygdaloid lesions.

Lesioned and non-lesioned rats did not exhibit a conditioned taste aversion on test day. This demonstrates that the amounts of alcohol consumed (0.89 g/kg; 0.97 g/kg; 0.99 g/kg in N, ABL and AL groups respectively) were too small to induce a conditioned aversion.

This ethanol induced aversion to an ethanol solution was obtained in Experiment 2. It was achieved by making the total dose of ethanol high enough: an ethanol injection followed the oral intake so as to make the total dose 2 g/kg. This dose was shown to be sufficient in intact rats to reinforce the spontaneous taste aversion to an ethanol solution. An enhanced aversion was also observed in lateral lesioned animals. By contrast, this acquired aversion was attenuated after basolateral nuclei lesions. This result is consistent with the attenuation of the LiCl induced saccharin aversion by basolateral amygdala lesion previously demonstrated by us and other investigators [1].

In Experiment 3, we have demonstrated the conditioned taste aversion induced by the postingestive effect of the oral intake of an ethanol-containing solution. The neophobic response on the first presentations of the ethanol-sucrose mixture in unlesioned rats did not allow the rats to ingest more than 1.3 g/kg alcohol. Again it was observed that the postingestive effect of this dose of alcohol did not induce a taste aversion. A C.T.A. to a flavored solution, induced by the oral ingestion of 1.2 g/kg of alcohol, has been demonstrated by Eckard [6]. But, in this case, conditioning was achieved by pairing the U.C.S. and C.S. for 4 consecutive days. The first pairings failed to produce a significant decrease in the intake of a flavored ethyl solution. This confirms that the one-trial learning of an ethanol aversion, as shown in our experiment, can only be obtained with a dose higher than 1.3 g/kg.

In lesioned rats the neophobic response was suppressed in ABL_{SE} rats and abolished in AL_{SE} rats, as is the case with the saccharin sweet tasting solution. This effect of lesions which contrast with the slight effect on a pure ethanol solution suggests that the sweet taste of sucrose entirely masks the taste of ethanol in the mixture.

After this suppression of neophobia due to basolateral nuclei lesions and because of the initial preference exhibited after lateral nuclei lesions, the initial intake of ethanol-sucrose solution in the two lesioned groups was very high (3 g/kg and 4.1 g/kg in ABL_{SE} and AL_{SE} groups respectively). As expected on the basis of a previous experiment, the process of association of postingestive effects with the taste of the solution was completely abolished in the basolateral

lesioned rats. On the contrary, a C.T.A. was achieved in laterally lesioned rats. However, in these animals, the induced aversion did not permanently limit the oral intake of alcohol and we observed successive increases and decreases in intake of the ethanol-sucrose solution.

These data provide new evidence for the role of conditioned taste aversion in the control and the limitation of oral intake of ethyl-alcohol solutions by rats. The fact that the basolateral lesion of the amygdala impairs the C.T.A. process suggests that a high and progressively increasing oral intake of ethanol could be obtained under single bottle ad lib conditions or under food restriction [23]. This induced-high voluntary intake of ethanol in rats through the suppression of toxicophobia could be used as a model in studies of dependence and tolerance acquired under chronic high oral intake of ethanol.

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