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Effects of Apomorphine, Clonidine or 5-Methoxy-NN-Dimethyltryptamine on Approach and Escape Components of Lateral Hypothalamic and Mesencephalic Central Gray Stimulation in Two Inbred Strains of Mice

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CAZALA, P. AND A. M. GARRIGUES. *Effects of apomorphine, clonidine or 5-methoxy-NN-dimethyltryptamine on approach and escape components of lateral hypothalamic and mesencephalic central gray stimulation in two inbred strains of mice.* PHARMACOL BIOCHEM BEHAV **18**(1) 87–93, 1983.—The effects of intraperitoneal injections of increasing doses of apomorphine, clonidine or 5-methoxy-NN-dimethyltryptamine (5-m-DMT) on approach and escape reactions induced by lateral hypothalamic (LH) or mesencephalic central gray (CG) stimulation were compared in BALB/c and DBA/2 mice. Apomorphine increased both the approach latency for LH stimulation and the escape latency for CG stimulation; the BALB/c strain was more reactive than DBA/2 animals. Clonidine reduced the approach latency for LH stimulation only in the BALB/c strain. 5-m-DMT increased escape latency both for LH and CG stimulation only in the DBA/2 strain. These results suggest that the neurochemical regulation of escape reactions respectively generated by LH or CG activation is partially different: dopamine seems to be involved only in CG aversion, whereas serotonin (5-HT) modulates both LH and CG escape reactions. Moreover, our results demonstrate a noradrenergic influence on the appetitive component of LH stimulation. Finally, they confirm that approach and escape reactions, particularly when induced from lateral hypothalamus, depend on distinct neuronal populations.

Appetitive and aversive responses Lateral hypothalamus Mesencephalic central gray Apomorphine Clonidine 5-Methoxy-NN-dimethyltryptamine BALB/c DBA/2 Mouse

THE intensity of the escape reaction in mice, induced by intracranial stimulation varies considerably from on strain to another. For instance, we have observed that BALB/c mice try to turn OFF self-administered electric stimulation of the lateral hypothalamus (LH) sooner than do DBA/2 mice [10]. Moreover, the escape reaction induced by stimulation of the dorsal region of the mesencephalic central gray (CG) is more intense in BALB/c than in DBA/2 mice [11].

The existence of reciprocal connections between LH and CG, as demonstrated by anatomical [16, 26, 41] and electrophysiological studies [5] could account for the similarities between these two aversive situations which involve a greater reactivity of the BALB/c mice in both cases.

One of the objectives of the present work was to determine whether the escape reactions induced by stimulation of these two cerebral structures were related to similar neurochemical mechanisms. Moreover, even though the stimulation applied to the dorsal part of CG has a strong aversive character, we have noticed, at least for certain current intensities, that this same stimulation is self-administered spontaneously by the two strains of mice. We have also tried to determine whether CG stimulation has a rewarding component as does LH stimulation. In order to attempt to answer these two questions, the effects of receptor agonists of the noradrenergic (clonidine), dopaminergic (apomorphine) and serotonergic (5-methoxy-NN-dimethyltryptamine: 5-m-DMT) systems on the behavioral responses induced by LH and CG stimulations in turn, were compared in the

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TABLE 1
STEREOTAXIC COORDINATES

Brain Structure	Strain	Antero-posterior (mm referring to interaural line)	Lateral (mm referring to sagittal line)	Vertical (mm from the surface of the skull)
LH	BALB/c	+1.90	±1.00	+5.60
	DBA/2	+2.00	±1.10	+5.30
CG	BALB/c	−0.55	±0.30	+2.90
	DBA/2	−0.50	±0.30	+2.80

BALB/c and DBA/c strains. The effects of specific drugs of the noradrenergic and dopaminergic systems were analysed because cerebral catecholamines seem to be involved in self-stimulation behavior [12, 15, 33], whereas serotonin (5-HT) appears to play a role in aversive processes [22, 25, 29].

The BALB/c-DBA/2 interstrain comparison was undertaken in this pharmacological study, in order to determine if the differences in behavioral reactivity observed between these strains during LH or CG stimulation result from neurochemical differences.

METHOD

Animals

The present experiments utilized 86 male mice of the DBA/2 Orl and of the BALB/c Orl strains, approximately 10 weeks of age.

Surgery

Under deep sodium thiopental anesthesia (DBA/2: 130 mg/kg, BALB/c: 90 mg/kg) the animals were stereotaxically implanted with a bipolar electrode made of two tightly twisted strands of 0.09 mm platinum wire. The electrode was implanted either in the ventral part of LH, or in the dorsal part of CG. The stereotaxic coordinates used are presented in Table 1.

Materials and Experimental Protocol

Behavior was studied in a 40×8×12 cm shuttle box [7]. A photoelectric cell was placed 7.5 cm from each end of the cage. By interrupting one photobeam the animal learned to trigger a continuous sinewave (100 Hz) stimulation, which stopped when the animal interrupted the beam at the other end of the cage. Automatic equipment recorded the time during which the mouse remained stimulated (ON duration) and non stimulated (OFF duration) with a precision of 0.01 sec. Daily sessions lasted 10 min. The total amount of time that stimulation was ON or OFF during the 10 min session was divided by the number of ON or OFF responses. The mean values of ON and OFF duration were determined. In order to produce very similar performance in the two strains the current intensities used were for LH stimulation: 6 to 10 μA in BALB/c mice and 10 to 15 μA in DBA/2 mice, and for CG stimulation: 10 to 14 μA in BALB/c mice and 16 to 22 μA in DBA/2 mice. These values were close to the threshold intensities which permit, for each of the two structures stimulated, the appearance of ON and OFF responses in both strains of mice [10,11].

The animals were run daily until their baseline response latencies had fully stabilized before a drug was administered.

On the first test day, the animals received an intraperitoneal injection of isotonic NaCl (control session). During the following days, they received an injection of increasing doses of apomorphine HCl, clonidine HCl or of 5-methoxy-NN-dimethyltryptamine (5-m-DMT). Different animals were used for each of the drugs. Apomorphine or clonidine were administered 10 min before a test session, whereas 5-m-DMT was injected immediately before a test session. Two successive injections in the same animal were separated by 72 hours. On the last day a second injection of NaCl was made.

Histology

At the end of the experiments, the animals were killed and their brains removed and fixed in a 10% formalin solution. Frontal frozen sections were made (40 μm) and stained with 0.1% thionin solution. Typical LH and CG stimulation sites are shown in Fig. 1.

RESULTS

At the current intensities applied, ON and OFF duration values were similar in BALB/c and DBA/2 animals during the control session (statistical comparison between the two strains: for LH implantations ON duration $t=0.76$ n.s., OFF duration $t=0.15$ n.s.; for CG implantations: ON duration $t=0.22$ n.s., OFF duration $t=0.86$ n.s.).

Furthermore the mean value of ON duration was similar for LH and CG implantations (BALB/c mice $t=0.89$ n.s., DBA/2 mice $t=0.65$ n.s.) whereas OFF duration was greater for CG than for LH implantations (BALB/c $t=4.40$, $p<0.001$; DBA/2 $t=4.38$, $p<0.001$).

Spontaneous activity was measured in non stimulated animals. The time spent in front or near each photoelectric cell was similar in the two strains studied, thus the baseline ON and OFF duration values were similar (ON duration (sec) BALB/c=34 (SEM±5), DBA/2=38 (SEM±5) $t=0.80$ n.s.; OFF duration (sec) BALB/c=36 (SEM±3), DBA/2=40 (SEM±6) $t=0.64$ n.s.) These data suggest that the differences observed between DBA/2 and BALB/c animals during

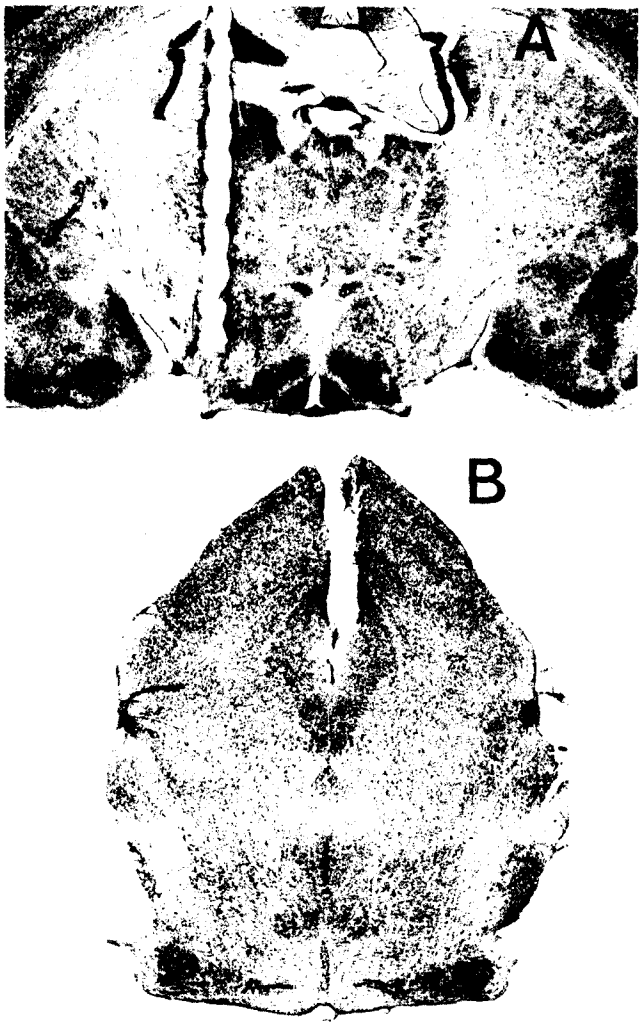

FIG. 1. Photomicrographs of thionin stained sections (40 μm) through LH (A) or CG (B) electrode tracks.

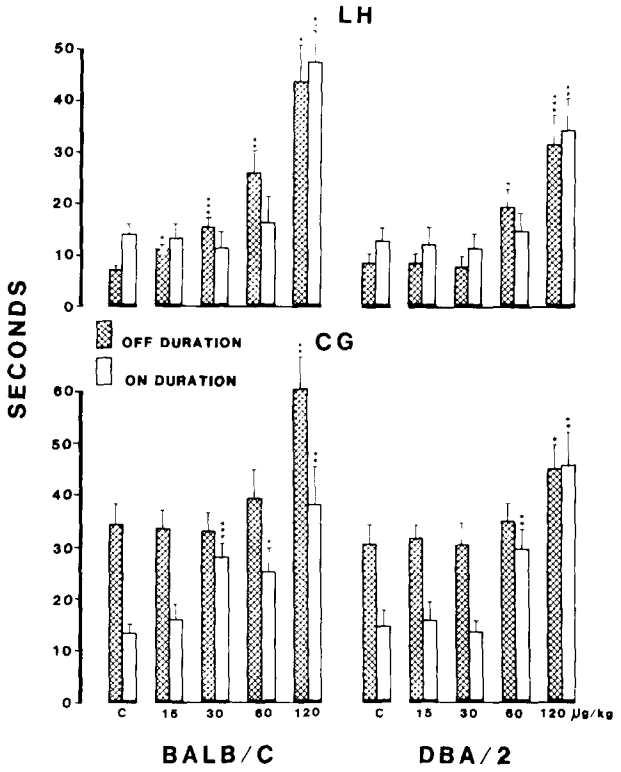

FIG. 2. Effects of injection of increasing doses of apomorphine on the latency of initiate (OFF duration cross-hatched bars) or on the latency to escape (ON duration open bars) lateral hypothalamic or mesencephalic central gray stimulation in BALB/c and DBA/2 mice (LH implantations: BALB/c N=8, DBA/2 N=8; CG implantations BALB/c N=8, DBA/2 N=8) C: control session (first NaCl injection) *$0.05>p>0.02$; **$0.02>p>0.01$; ***$0.01>p>0.001$ (Student's t-test).

our pharmacological analysis are not related to variations in motor capacities.

Effects of Apomorphine

The results obtained are summarized in Fig. 2.

Lateral hypothalamus. Apomorphine did not affect ON duration in either strain except at the highest dose injected (120 μg/kg). The increase observed, which corresponds to a parallel increase in the OFF duration value, was probably nonspecific. As Wauquier and Niemegeers [39] have suggested, this response inhibition could be due to a non-physiological activation of dopaminergic receptors with interruption of integrated behaviour.

On the other hand, apomorphine specifically increased the OFF duration in BALB/c mice at 15, 30 and 60 μg/kg and in DBA/2 mice only at 60 μg/kg. This difference was confirmed by an analysis of variance of two factors, strain and drug dose, the latter being a repeated measure [40]: difference between the strains, $F(1,14)=11.57$; $0.01>p>0.001$; difference between the effect of the three doses, $F(2,28)=18.30$, $p<0.001$; strain × dose interaction, $F(2,28)=2.05$, n.s.

OFF duration was unaltered at these doses; the calculation of a correlation coefficient for ON and OFF duration yielded these values: BALB/c: r=0.20, n.s.; DBA/2: r=−0.16, n.s.

Mesencephalic central gray. Concerning CG, apomorphine seemed to modulated specifically the escape reactions engendered by stimulation of the dorsal part of this brain structure.

Indeed at 30 and 60 μg/kg in BALB/c mice and only at 60 μg/kg in DBA/2 mice, the mean value of ON duration increased. Moreover, the effects of increasing doses of apomorphine in BALB/c and DBA/2 mice were not identical (strain effect: $F(1,14)=6.45$; $0.02>p>0.01$; dose effect, $F(2,28)=48.97$; $p<0.001$; strain × dose interaction, $F(2,28)=36.02$; $p<0.001$). No alteration of OFF duration was observed at the first three doses (correlation coefficients for ON and OFF values: BALB/c: r=−0.15, n.s.; DBA/2: r=−0.33, n.s.).

As with LH stimulation we observed that an higher dose of apomorphine (120 μg/kg) increases simultaneously ON and OFF duration values in both strains of mice.

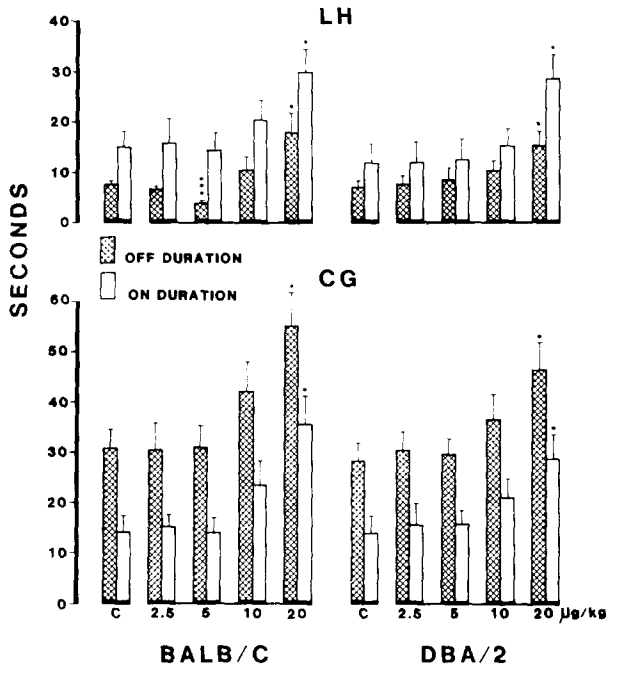

FIG. 3. Effects of injection of increasing doses of clonidine on the latency to initiate (OFF duration cross-hatched bars) or on the latency to escape (ON duration open bars) lateral hypothalamic or mesencephalic central gray stimulation in BALB/c and DBA/2 mice (LH implantations BALB/c N=6, DBA/2 N=6; CG implantations BALB/c N=6, DBA/2 N=6) C: control session (first NaCl injection) *$0.05>p>0.02$; ***$0.01>p>0.001$ (Student's t-test).

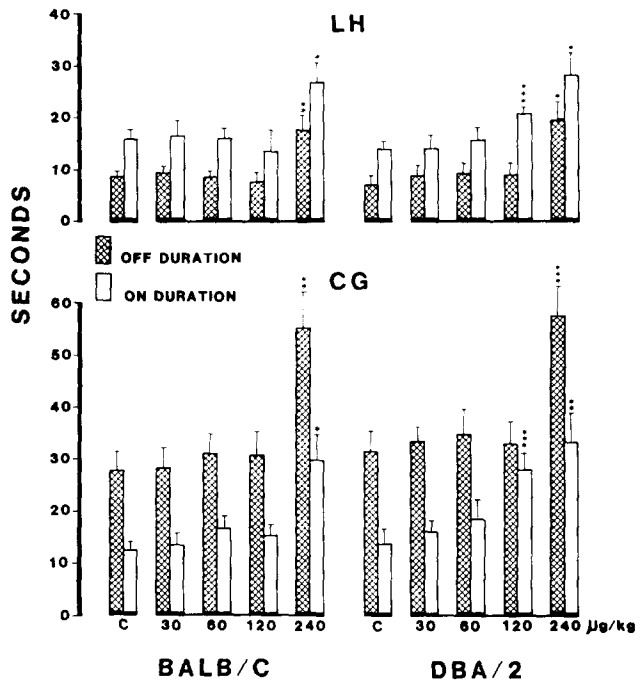

FIG. 4. Effects of injection of increasing doses of 5-methoxy-NN-dimethyl-tryptamine on the latency to initiate (OFF duration cross-hatched bars) or on the latency to escape (ON duration open bars) lateral hypothalamic or mesencephalic central gray stimulation in BALB/c and DBA/2 mice. (LH implantations BALB/c N=7, DBA/2 N=8; CG implantations BALB/c N=7, DBA/2 N=8) C: control session (first NaCl injection) *$0.05>p>0.02$; **$0.02>p>0.01$; ***$0.01>p>0.001$. (Student's t-test).

Effects of Clonidine

The results of this experiment are summarized in Fig. 3.

Lateral hypothalamus. In BALB/c strain, a low dose of clonidine (5 µg/kg) greatly decreased approach latency ($t=5.11$, $0.01>p>0.001$). This phenomenon was not observed in DBA/2 mice (analysis of variance confirmed that for the doses in the 2.5 to 10 µg/kg range, clonidine had not the same effects in the two strains: strain effect, $F(1,10)=8.80$, $0.02>p>0.01$; dose effect, $F(2,20)=5.52$, $0.02>p>0.01$; strain × dose interaction, $F(2,20)=3.66$, $0.05>p>0.02$). In BALB/c strain, the correlation coefficient for ON and OFF values at the dose 2.5 and 5 µg/kg was $r=-0.14$, n.s.

The highest dose injected (20 µg/kg) increased simultaneously the mean value of ON and OFF duration in both strains of mice; it seems that these effects are nonspecific and probably related to the sedative influence of the drug.

Mesencephalic central gray. For the doses in the 2.5 to 10 µg/kg range, clonidine had no important effects in BALB/c and DBA/2 animals (comparison between the two strains: ON duration, $F(1,10)=1.18$, n.s.; OFF duration $F(1,10)=1.04$, n.s. Only nonspecific alterations (i.e., sedative effects) were observed in the two strains at 20 µg/kg.

Effects of 5-m-DMT

Figure 4 summarizes the results obtained.

Lateral hypothalamus. Specific alteration induced by 5-m-DMT, that is an increase in escape latency at 120 µg/kg, was only observed in the DBA/2 strain. Statistical analysis of the data from the first three doses confirmed that BALB/c and DBA/2 animals reacted differently to 5-m-DMT: strain effect, $F(1,13)=4.97$, $0.05>p>0.02$; dose effect $F(2,26)=5.03$, $0.02>p>0.01$; strain × dose interaction, $F(2,26)=18.68$, $p<0.001$. The increase in escape latency observed in the DBA/2 strain was induced without concomitant modification of approach latency ($r=-0.19$, n.s.).

The highest dose injected (240 µg/kg) induced tremor and ataxia as in the rat [35]. This phenomenon might explain why ON and OFF duration values increased simultaneously at this dose.

Mesencephalic central gray. As for LH stimulation, specific effects induced by 5-m-DMT were only observed in DBA/2 strain in which escape latency increased after injection of 120 µg/kg. The difference observed between BALB/c and DBA/2 was statistically significant (For the doses in the 30 to 120 µg/kg range: strain effect, $F(1,13)=5.55$, $0.05>p>0.02$; dose effect, $F(2,26)=6.19$, $0.01>p>0.001$; strain × dose interaction $F(2,26)=8.88$, $0.01>p>0.001$). As for LH stimulation, no concomittant alteration of approach latency was observed ($r=-0.17$, n.s.).

It is interesting to note that when the animals received the second injection of NaCl, at the end of each experiment, ON and OFF values were similar to those recorded during the first control session.

DISCUSSION

In the behavioral model used in our pharmacological analysis, the continuous electrical stimulation is spontaneously triggered and interrupted by the animals. Various data have indicated that, under certain experimental conditions, the latency to initiate the stimulus (OFF duration) may be considered an index of its rewarding effect, whereas the latency to terminate it (ON duration) is an index of its aversive effect [3, 4, 10, 19]. The results of our pharmacological study lead to the following conclusions:

First, as the results obtained after injection of apomorphine demonstrate, it seems that escape responses generated by LH or CG stimulation depend on partially different neurochemical substrates: only CG aversion decreased significantly during the activation of dopaminergic receptors. This phenomenon was observed in both strains but appeared sooner in the BALB/c mice. Furthermore, it appears that serotonergic mechanisms are involved in the control of these two aversive responses.

For both LH and CG, the injection of 5-m-DMT, an agonist of pre- and post-synaptic serotonergic receptors, was followed by increases in escape latency in DBA/2 mice, which suggested that this drug decreased the aversive effects of electrical stimulation. These results confirm other observations demonstrating the role of 5-HT in the regulation of escape responses induced by electrical stimulation of different cerebral structures: injection of 5-hydroxytryptophan, a precursor of 5-HT [21,29] of 5-m-DMT [30] or local perfusion of 5-HT [25] decreased the escape responses. On the other hand, a global decrease of 5-HT level, produced by injection of PCPA, is followed by an increase in escape response induced by CG stimulation [22].

The fact that changes caused by 5-m-DMT injections appeared only in DBA/2 could be due to a greater density and/or greater reactivity of serotonergic receptors in this strain. This factor may also explain the greater escape latency that this strain shows, in response to continuous stimulation of the LH or CG [10,11].

Second, two opposing phenomena are observed in the case of the LH with respect to intensity of approach reactions. Apomorphine, when administered in doses which do not disturb locomotor activity, increases the approach latency in the two strains. This fact, which would seem to indicate an attenuation of the rewarding effect of LH stimulation, has already been observed during standard self-stimulation in mice which were implanted in the ventral part of the LH [9]. The greater sensitivity of BALB/c to apomorphine, already noted in the case of CG aversion, perhaps could be explained by a recent observation of Boehne and Ciaranello [6] who have shown that brain dopaminergic receptors are more numerous in the BALB/c strain than in the DBA/2 strain. It is important to note that the behavioral modifications observed in the present work were induced by doses of apomorphine below the lowest stimulant doses found effective as putative post-synaptic agonist during studies on self-stimulation in the rat [17,39].

Moreover, the fact that small doses of clonidine (5 μg/kg) decreased considerably the approach latency of BALB/c may indicate that this drug increases the rewarding effect of LH stimulation. This behavioral facilitation, previously observed at the same dose during self-stimulation by lever pressing [8] is more difficult to explain.

Clonidine, which selectively stimulates central α-noradrenergic receptors, generally has a sedative effect on exploratory [24,34] and locomotor activity [42] sometimes at low doses [37], and on self-stimulation behavior in rats [17, 19, 38] and monkeys [31]. Even so, high doses of clonidine induce hyperactivity in animals which have previously received injections of substances such as reserpine and apomorphine [1,2] or 6-hydroxydopamine plus reserpine [42].

To explain these two sets of data it has been suggested that the sedative effects correspond to an action of clonidine on pre-synaptic α_2 receptors [13,32] and that hyperactivity observed after pharmacological treatment is the result of activation of the central post-symaptic α_1 receptors [13,27]. In any case, very small amounts of clonidine seem to increase locomotor activity in the rat [18] and facilitate self-stimulation in mice [8]. Also, Koss and Christensen [23] have shown that small amounts of clonidine can induce central post-synaptic effects. According to results recently obtained by U'Prichard *et al.* [36] dorsal noradrenergic bundle lesions by 6-hydroxydopamine raise significantly the number of α_2 receptors with high affinity for clonidine in the cortex, but decrease the level in other structures such as the amygdala. The high affinity α_2 receptors could be either post- or pre-synaptic.

The behavioral facilitation that we observed in BALB/c after injection of 5 μg/kg of clonidine could correspond to an activation of the α_2 post-synaptic receptors. The sedative effects observed at larger doses could, on the other hand, result from the activation of the α_2 pre-synaptic receptors, which could confirm the results obtained by Franklin and Herberg [14] and by Hunt *et al.* [20] who identified a presynaptic action of clonidine in self-stimulation in the rat.

Even if it is the case that activation of dopaminergic or noradrenergic receptors influences the intensity of approach reactions with LH stimulation, it seems less likely for mesencephalic stimulation. CG approach may be linked to a catecholaminergic activation, since catecholaminergic innervation (probably arising from the dorsal noradrenergic bundle) has been discovered in CG near the cerebral aqueduct [28]. However, it is possible that catecholamine receptor agonists are not able to modulate the small "rewarding component" of CG stimulation. New pharmacological experiments are now in progress in order to elucidate the neurochemical mechanisms underlying CG approach.

In order to produce similar baseline responding, the current intensities were different for each structure and for each strain. This difference raises the possibility that the drug effects might be different depending on the current levels used for the two strains and the two areas. Our results suggest that there is no obvious correlation between the current intensities applied and sensitivity to the drugs administered. For instance, the BALB/c strain, in which the lowest intensities were used, was more sensitive to apomorphine and clonidine than the DBA/2 strain, but did not react to 5-m-DMT. Moreover, it might be suggested that the use of higher current intensities in the case of CG stimulation could lead to increased sensitivity to apomorphine during ON time. This hypothesis would seem to be invalidated, since in both LH and CG, ON duration is increased by an identical dose of 5-m-DMT.

Third, this research also demonstrated that it is possible by pharmacological means to modify independently the intensity of approach and escape reactions due to LH stimulation. These observations which confirm those of Atrens *et al.* [4] and Hunt *et al.* [19] suggest that the two components of LH stimulation result in fact from activation of distinct neuronal populations.

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