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Different Effects of Apomorphine on Climbing Behavior and Locomotor Activity in Three Strains of Mice

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CABIB, S. AND S. PUGLISI-ALLEGRA. *Different effects of apomorphine on climbing behavior and locomotor activity in three strains of mice.* PHARMACOL BIOCHEM BEHAV **23**(4) 555–557, 1985.—Apomorphine (0.1, 0.25, 0.5, 1, 3 mg/kg, SC), induces a dose-dependent reduction of locomotor activity in DBA/2(DBA) and BALB/c(BALB) mice, while it enhances locomotor activity in a biphasic way in C57BL/6(C57) mice. On the other hand, apomorphine is ineffective in modifying climbing behavior in DBA mice while it increases climbing behavior in C57 and BALB mice. The results, taken together, suggest that these are two different behaviors, possibly controlled by different dopaminergic mechanisms depending on the genetic makeup.

Locomotor activity Climbing Apomorphine Inbred mice

THE search for antipsychotic and antiparkinsonian agents devoid of central nervous system side effects has given new impulse to the study of the dopaminergic system [9]. Recent evidence has suggested that different dopaminergic agents may act on multiple populations of dopamine (DA) receptors located in different brain structures [4,9]. Most of the behavioral evidence collected in this regard come from the study of apomorphine-induced stereotyped behavior in the rat. Apomorphine, in fact, induces in this species a repetitive occurence of classes of stereotypic behaviors that are dose-dependent. It has been shown by the technique of intracerebral injection of DA agonists that different brain regions of the rat forebrain are involved in the various classes of behaviors [4,9].

Pharmacological studies of dopaminergic-controlled behavior in the mouse have mainly utilized two tests: measurement of horizontal locomotor activity [1, 6, 15] and climbing behavior [5, 8, 14, 16]. Both tests allow easy behavioral scoring and are reliable in detecting the effects of pharmacological manipulation of brain DA systems. Nonetheless, it is still unclear if the two tests measure the same behavior, namely locomotion, as some authors suggest [5], or two different classes of behavior [13]. On one side, in fact, it has been shown that climbing behavior is enhanced by DA agonists which stimulate locomotor activity and is depressed by low doses of apomorphine which are known to decrease locomotion [8,14]. On the other, the powerful locomotor stimulant amphetamine is only able to induce a weak climbing and active doses of non dopaminergic drugs which affect horizontal activity are totally unable to modify this behavior [8,14].

The lack of clarity on this point may limit the usefulness of these tests especially in light of the results obtained in the rat. The purpose of this work was to verify if the two tests measure different behaviors by comparing the effects of apomorphine on climbing behavior and locomotor activity in three strains of mice: DBA/2, C57BL/6 and BALB/c. The use of inbred strains of mice which have been extensively investigated for a number of neurochemical parameters related to the DA systems [3, 7, 10, 18, 19] may be, in fact, a useful tool for elucidating differences or similarities between the two behaviors.

METHOD

Subjects were naive BALB/c (IFFA CREDO, L'Arbesle, France) DBA/2, and C57BL/6 (Charles River, Calco, Como, Italy) mice weighing 25–28 g. The mice were mantained with food and water ad lib in a 12/12 hr light-dark cycle (lights were on from 07.00 to 19.00 hr) and tested always during the second half of the light period (between 14.00 and 16.00 hr).

Locomotor activity was measured as previously described [17], by an automated apparatus consisting in eight toggle-floor boxes, each divided into two 20 × 10 cm compartments connected by a 3 × 3 cm opening. For each mouse, the number of crossings from one compartment to the other was recorded by means of a microswitch connected to the tilting floor of the box. Climbing behavior was scored by a trained observer as previously described [2]. The observer did not know which treatment was given to the tested animals. Animals were put into individual cylindrical cages (12 cm diameter, 14 cm high, with walls of vertical metal bars, 22 mm diameter, 1 cm apart surmounted by a smooth surface). The behavior was scored as follow: 4 paws on the floor (0); forefeet holding the bars (1); 4 paws holding the bars (2).

Both tests were carried out in sound proof cubicles where a 30 W lamp was the only source of illumination. The

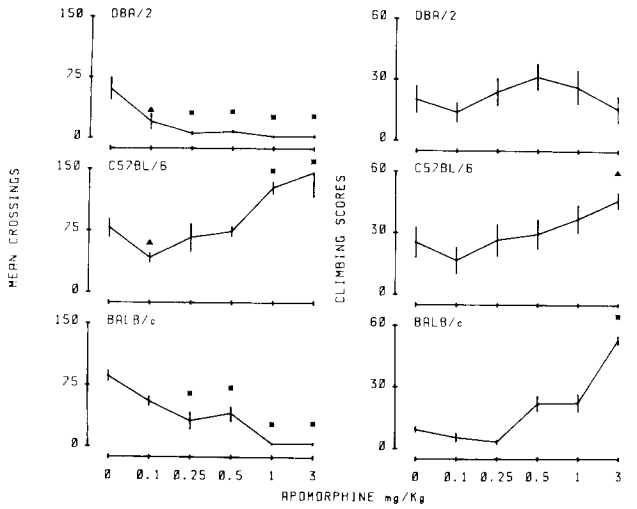

FIG. 1. Effects of apomorphine on locomotor activity and climbing behavior of DBA, C57, and BALB mice. Results are expressed in terms of number of crossings (mean ± S.E.) and climbing scores (mean ± S.E.). ▲$p<0.05$ and *$p<0.01$ when compared with saline groups.

temperature of the cubicles was constant. Testing sessions started 5 min after treatment and lasted 60 min. Mice were injected with different doses (0.1, 0.25, 0.5, 1, 3 mg/kg) of apomorphine hydrochloride (Sigma) dissolved in saline (0.9% NaCl) immediately before use, or with saline alone. All injections were made subcutaneously (SC) in a volume of 10 ml/kg. Experimental groups consisted of 8 mice (locomotor activity) or 12 mice (climbing behavior) and each group was tested one time only.

For each behavior, data were statistically analyzed by two factor analysis of variance (ANOVA), the factors being strain (three levels: DBA, C57, BALB) and treatment (6 levels: saline and apomorphine 0.1, 0.25, 0.5, 1, 3 mg/kg). Further analysis for individual between-group comparisons was carried out with post hoc tests (Duncan multiple range test).

RESULTS AND DISCUSSION

Concerning locomotor activity, ANOVA showed a significant strain main effect, $F(2,126)=78.39$, $p<0.001$, a significant drug treatment main effect, $F(5,126)=5.91$, $p<0.001$, and a strain × drug treatment interaction, $F(10,126)=11.28$, $p<0.001$. Within each strain, individual between-group comparisons showed significant differences between saline and apomorphine injected mice. Apomorphine at all doses used significantly decreased locomotor activity in DBA mice. Apomorphine doses of 0.25 through 3 mg/kg also reduced the locomotor response in BALB animals; while in C57 mice apomorphine had a biphasic effect, with the lowest dose inhibiting locomotor activity and the highest (3 mg/kg) enhancing it (Fig. 1).

Concerning climbing behavior, ANOVA showed a significant strain main effect, $F(2,198)=6.02$, $p<0.001$, a significant drug treatment main effect, $F(5,198)=9.18$, $p<0.001$, and a strain × drug treatment interaction, $F(10,198)=3.57$, $p<0.001$. Within each strain, individual-between group comparisons showed significant differences between saline and apomorphine injected mice in C57 and BALB strains at the highest apomorphine doses while no significant differences were evident in DBA strain (Fig. 1).

The present results show that in our experimental conditions climbing behavior and locomotor activity are differently modulated by the dopaminergic agonist apomorphine in different mouse strains. In fact, locomotor activity of DBA mice was significantly depressed by all doses of apomorphine used in this experiment. However apomorphine was unable to modify significantly climbing behavior in this strain confirming previous results [11]. Also the response of the BALB strain to apomorphine in the locomotor activity test (decrease) was opposite to that shown by the same strain in the climbing test (increase). Only C57 mice presented a similar pattern of response to the drug in both tests; however, this seems to be the only strain to show an apomorphine-induced increase in locomotor activity as previously described [12,17].

Major strain differences in the effects of apomorphine on the two tests suggest that the genotype plays some role in the dopaminergic modulation of these behaviors. Also in this case, there seems to be a lack of correlation between the two behaviors. In fact, apomorphine at a dose of 3 mg/kg depressed locomotor activity in BALB and DBA mice, but had an opposite effect on C57 mice ($p<0.01$ when compared with DBA and BALB by the Duncan test). Similarly apomorphine activated BALB and C57 mice without affecting DBA mice ($p<0.01$ when compared with C57 and BALB mice by the Duncan test) in the climbing test.

It must be pointed out that other forms of stereotyped behavior were absent or very rare at all apomorphine doses and in all strains tested in this experiment. Some discontinuous sniffing was observed at the highest doses in all strains and some biting and licking were elicited by the highest dose of apomorphine in the DBA mice. These other classes of behavior, however, became more evident at higher doses and interfered with climbing and locomotion overlapping with them. As apomorphine dose was increased the orofacial stereotypic responses occurred predominantly ([5,19], unpublished observations). This is not surprising since it is known that in the rat different classes of stereotypic behavior are elicited by different doses of dopaminergic agonists [4,9].

Taken together these results support the hypothesis that horizontal locomotion and climbing are distinct behaviors possibly mediated by different dopaminergic mechanisms. Further researches should clarify the extent to which these genotypic differences are accounted for by pharmacokinetic (absorption, distribution, biotransformation excretion of apomorphine) or pharmacodynamic (receptors) interactions. If pharmacodynamic interactions account for most of the observed differences then future experiments may establish if and how different dopaminergic pathways and/or receptor types as well as other neurotransmitter systems are involved in the control of these two behaviors.

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