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Effect of Clonidine, Amphetamine, and Their Combinations on the Locomotor Activity of CD-1 and C57BL/6 Mice

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HANO, J., J. VETULANI, M. SANSONE AND A. OLIVERIO. *Effect of clonidine, amphetamine, and their combinations on the locomotor activity of CD-1 and C57BL/6 mice.* PHARMAC. BIOCHEM. BEHAV. 9(6) 741–746, 1978.—Clonidine inhibited the exploratory motor activity of C57BL/6 mice non-habituated to the testing conditions. In CD-1 mice clonidine did not depress exploratory activity but did elevate the basal locomotor activity of animals both non-habituated and habituated to testing conditions. Amphetamine increased the locomotor activity of many C57BL/6 mice and conversely inhibited the locomotion of many CD-1 mice. In both strains, amphetamine in doses up to 2 mg/kg was unable to alter effects produced by clonidine. Results suggest that the locomotor activity of C57BL/6 mice is more sensitive than that of CD-1 mice to drugs affecting the central noradrenergic system.

Interstrain differences Amphetamine Locomotor activity CD-1 mice Clonidine C57BL/6 mice

CLONIDINE is a drug with a wide spectrum of activity. It produces sedation, EEG synchronization and sleep in man [11], cat [14,17], rabbit [14,17], rat [14, 17, 20], mouse [13, 24] and chicken [13,17], but only weak sedation was observed in the guinea pig [12]. Most of these data were obtained from experiments in which naive animals were tested after a certain interval following clonidine injection, and the measurements started immediately after the animal had been placed in an unfamiliar testing environment. It is interesting that rats habituated to an actometer increased locomotor activity following clonidine administration [6]. Clonidine was therefore concluded to inhibit exploration but elevate basal locomotor activity in rats [5,6].

Relating the behavioral effects of clonidine to its receptor actions is difficult. The drug is primarily regarded as an alpha-adrenoceptor agonist [15,19], but it also affects the serotonergic system [1, 22, 28, 30, 37] and stimulates cerebral epinephrine [8,16] and histamine H_2 receptors [3, 4, 18]. It has been suggested that clonidine preferentially stimulates presynaptic alpha-adrenoceptive sites, which may account for the inhibition of noradrenergic transmission by the drug [34,35]. This overall inhibitory effect might be responsible for the inhibitory action of clonidine on locomotor activity [36].

However, a direct stimulatory action of clonidine on postsynaptic alpha-adrenoceptors has also been reported. The potentiation by clonidine of the flexor reflex of the spinal rat [2] and hypermotility observed after administration of clonidine to centrally chemosympathectomized rats pretreated with reserpine or yohimbine [40] have been attributed to the stimulatory action of the drug on central postsynaptic alpha-adrenoceptors. There have also been contrary reports indicating a postsynaptic inhibitory action of clonidine on central adrenoceptors in the brain cortex and the limbic system of the rat, as clonidine inhibited the norepinephrine-induced rise in the level of cyclic AMP in tissue slices from these brain areas [31,39].

Genetically homogenous and well characterized inbred mouse strains represent a very useful tool in studies on psychotropic drugs, particularly on relations between behavioral and biochemical effects and sources of variability of responding [10,27]. A number of inbred strains are known for certain behavioral patterns ranging from various levels of spontaneous activity to increased learning performance [9, 26, 33]. The behavioral characteristics of the C57BL/6 strain were described in detail earlier [32]. Recent findings [29] suggest that mice of this strain are particularly sensitive to the effects of drugs acting on central adrenergic systems. In addition, the striatal dopamine-dependent adenylate cyclase in C57BL/6 mice is responsive to dopaminergic stimulation and morphine administration in this strain produces a running fit concurrent with an elevation of the striatal cyclic AMP level [38].

Because of these data C57BL/6 mice were used in this study together with a randombred strain of mice, CD-1. In addition to the evaluation of effects of clonidine alone on motor activity, the effects of amphetamine and clonidine-amphetamine combinations were also tested. Previously [39], clonidine and amphetamine had been observed to exert a mutually antagonistic action on self-stimulation of the me-

dian forebrain bundle in the rat. The following experiment was carried out in order to determine if a similar mutually antagonistic effect of clonidine and amphetamine would be exerted on the locomotor activity of the mice.

METHOD

Inbred C57BL/6 mice and randombred CD-1 mice were purchased from Charles River (Calco Como), and were kept under standard laboratory conditions for at least one week before testing. Ambient temperature was 23°C and a 12 hr dark-light cycle was maintained. Animals had free access to food (Charles River) and tap water and were housed 8 to a 24×17×14 cm on macrolon cage.

Locomotor activity was measured in a box apparatus, 40×10×10 cm, divided in the middle by a partition. The two compartments were connected by a 3×3 cm opening in the partition, at floor level. Microswitches placed under the pivoted grid floor were activated by crossing the opening and impulses were recorded with an Esterline Angus operation recorder. The apparatus was placed in a sound-insulated, illuminated cabinet.

Naive mice were injected IP twice, 75 and 15 min before placing them in the apparatus. Saline or 0.2 or 0.5 mg/kg clonidine was given in the first injection, and saline or 1 or 2 mg/kg amphetamine in the second. The locomotor activity was measured for 30 or 60 min. Each experimental group consisted of 6–8 mice unless stated differently.

Habituated animals which were previously tested at least one week earlier under saline/saline treatment or not tested at all were habituated by being placed in the apparatus for at least 1 hr. They were then briefly removed for injection of saline or 0.5 mg/kg clonidine and placed back again. Locomotor activity was then recorded for 3 hr. Each group consisted of 8 mice.

Clonidine hydrochloride (courtesy of Boehringer Sohn, Ingelheim) and DL-amphetamine hydrochloride (K and K Labs, Inc., Plainview, NY) were dissolved for administration in saline and distilled water, respectively. All injections were given intraperitoneally in a volume of 10 ml/kg.

Data were analyzed by the appropriate analysis of variance and between-group comparisons were, if applicable, made by one-way analysis of variance.

RESULTS

Non-habituated–naive mice. The results obtained with the randombred CD-1 strain were variable and the results of two experiments carried out approximately one month apart were significantly different. In the first experiment the mice displayed low initial (exploratory) activity (24.1 ± 1.8 crossings per 10 min, N=16), and their overall activity declined rapidly. In the second experiment the initial locomotor activity was higher by 60% (38.1 ± 2.5 crossings per 10 min) and the decline in locomotor activity was slow (compare control curves in Figs. 1 and 2). Inbred C57BL/6 mice showed less pronounced differences in the initial locomotor activity, but the rate of decline of motility in the two experiments was also different. The analysis of variance carried out on combined results demonstrated that a significant difference between the strains existed only in the first 10 min period, suggesting that the C57BL/6 mice showed a lower exploratory activity than CD-1 mice, $F(1,53)=5.37$.

Since differences were observed in the locomotor activity of different control groups, the groups of experimental animals were always compared with their own concurrently tested controls in the analysis of the data.

Effect of clonidine in CD-1 and C57BL/6 mice. The dose of 0.1 mg/kg clonidine was ineffective in changing the locomotor activity of mice of either strain. The dose of 0.2 mg/kg did not affect the exploratory activity of CD-1 mice but significantly elevated the locomotor activity at subsequent time intervals (Fig. 1). The same dose in C57BL/6 mice significantly inhibited the exploratory activity, and slowed down the rate of decrease in locomotor activity, as compared with control mice (Fig. 1).

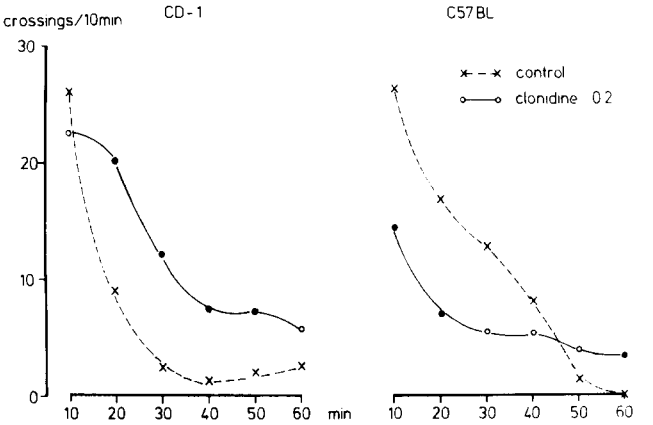

FIG. 1. The effect of 0.2 mg/kg clonidine on the changes in locomotor activity of naive CD-1 and C57BL/6 mice. The mice were injected with clonidine or saline 75 min before the test, and were placed in the actometer at time 0. Full circles denote a statistically significant ($p<0.05$) difference in comparison with the control value at the same time interval. Each point represents the mean of 8 results (16 results for CD-1 control group).

The dose of 0.5 mg/kg clonidine inhibited significantly the exploratory activity (during the first 10 min interval) of both strains (Fig. 2). The effect was particularly strong in C57BL/6 mice, in which the locomotor activity was brought down to the basal activity level. The inhibitory effect in CD-1 mice was much less pronounced and at subsequent time intervals the locomotor activity was maintained at a high level (Fig. 2).

The results are summarized in Fig. 3, in which the locomotor activity of mice (number of crossings) during the first 20 min interval was assumed to be the exploratory activity, while the basal activity was defined as the number of crossings between the 20th and 60th min of the test. As illustrated in Fig. 3, clonidine in CD-1 mice did not affect initial exploratory activity but did significantly elevate the basal level activity. In C57BL/6 mice the drug inhibited exploration without affecting the basal locomotor activity level.

Effects of amphetamine. CD-1 mice responded to amphetamine in an unpredictable way. Although 0.5 mg/kg amphetamine increased the locomotor activity during the first 10 min interval (by 35%, $p<0.05$), the 1 mg/kg dose produced an unexpected inhibition of exploratory and overall activities in 40% of mice. A CD-1 mouse was considered inhibited if it crossed the partition less than 15 times within the first 10 min

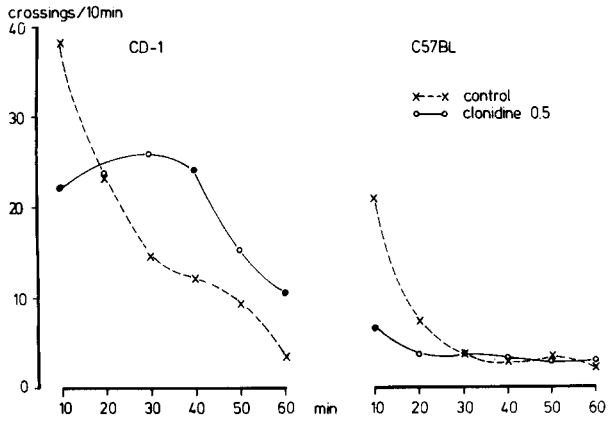

FIG. 2. The effect of 0.5 mg/kg clonidine on the changes in locomotor activity of naive CD-1 and C57BL/6 mice. Each point is the mean of 6–8 results (16 results for CD-1 control group). For other explanations see Fig. 1.

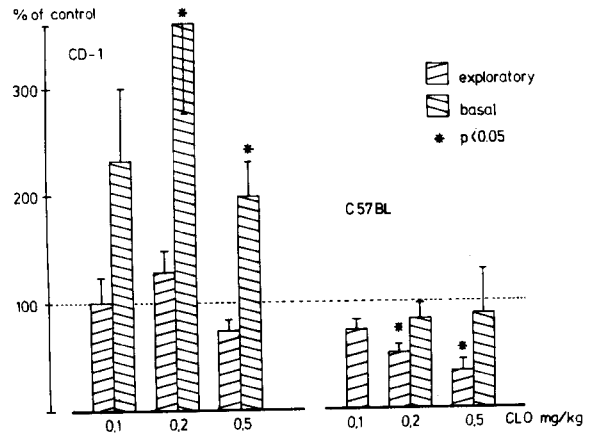

FIG. 3. The effect of clonidine on exploratory and basal activities of CD-1 and C57BL/6 mice. Exploratory activity is defined as the number of crossings during the first 20 min of the test. The basal activity is the number of crossings between 20th and 60th min of the test. The results are presented as percentages of concurrently tested controls. Each bar represents the mean ± SEM of 6–8 results.

and less than 40 times during 1 hr. The same doses of amphetamine produced locomotor stimulation in C57BL/6 mice. Figure 4 presents the spectra of action of 1 mg/kg amphetamine on the exploratory activity in both strains of mice. As illustrated, amphetamine shifted the distribution of locomotor activity to the left in CD-1 mice, while for C57BL/6 mice the distribution became bimodal with some mice reacting similarly to controls and others responding with locomotor stimulation.

Results for 2 mg/kg amphetamine are illustrated in Fig. 5. This dose did not significantly affect the locomotor activity of CD-1 mice but did produce a significant stimulation of the exploratory activity in C57BL/6 mice.

Effects of clonidine-amphetamine combinations. Amphetamine, 2 mg/kg, did not change the effects of 0.5 mg/kg clonidine on the locomotor activity in CD-1 mice. The

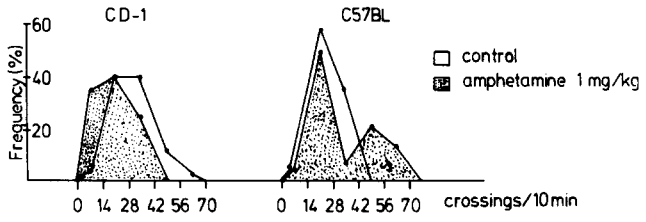

FIG. 4. Frequency distribution of the number of crossings for CD-1 and C57BL/6 mice receiving 1 mg/kg DL-amphetamine. The test period lasted 10 min. The groups consisted of 20 (CD-1) or 14 (C57BL/6) mice.

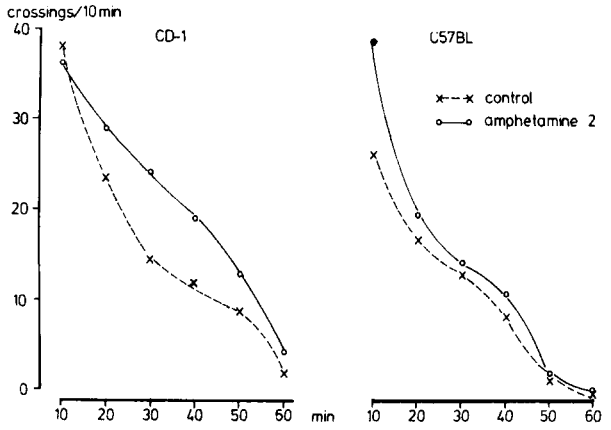

FIG. 5. The effect of 2 mg/kg amphetamine on the changes in locomotor activity of naive CD-1 and C57BL/6 mice. DL-Amphetamine or saline was injected 15 min before the test. Each point represents the mean of 6–8 results (16 results for CD-1 controls). The full circle represents a result significantly different ($p<0.05$) from the respective control value.

locomotor activity of these mice receiving clonidine alone or in combination with amphetamine changed with time according to the same pattern, unlike the pattern observed after amphetamine alone, as indicated in Fig. 6. Similarly, in C57BL/6 mice the effects of 0.2 mg/kg clonidine were not significantly altered by a subsequent injection of 2 mg/kg amphetamine, as indicated in Fig. 7.

Effects of clonidine on habituated mice. In habituated CD-1 mice 0.5 mg/kg clonidine significantly elevated the locomotor activity between the 1st and 2nd hr after the administration. In C57BL/6 mice clonidine initially significantly depressed the already low basal locomotor activity. These effects are illustrated in Fig. 8.

DISCUSSION

The present experiment shows that the CD-1 and C57BL/6 mice react differently to clonidine and amphetamine, drugs that affect central noradrenergic transmission. In C57BL/6 mice clonidine depressed exploratory locomotor activity in a dose-dependent manner. Conversely, CD-1 mice did not respond to lower doses of clonidine with a depression of exploratory activity. However, these mice

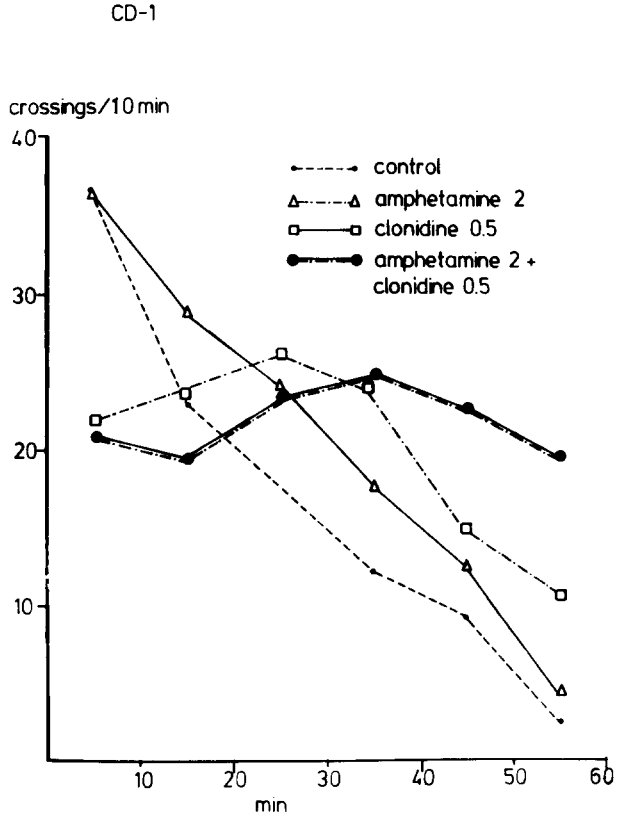

FIG. 6. The effect of a combination of 0.5 mg/kg clonidine and 2 mg/kg amphetamine on the changes in locomotor activity of naive CD-1 mice. Clonidine was given 75, and amphetamine 15 min before the test. Each point represents the mean of 5–8 results (16 results for the control group).

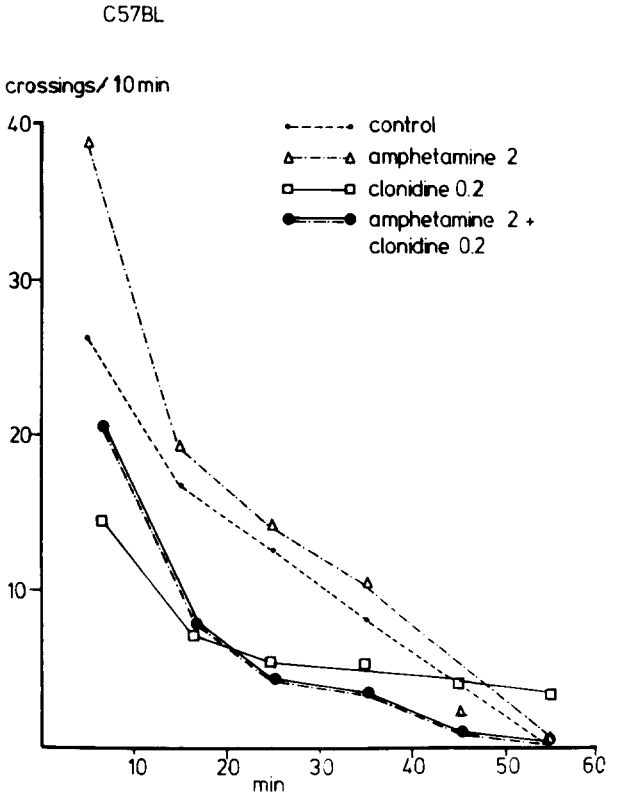

FIG. 7. The effect of a combination of 0.2 mg/kg clonidine and 2 mg/kg amphetamine on the changes in locomotor activity of naive C57BL/6 mice. Each point represents the mean of 8–12 results. For other explanations see Fig. 6.

exhibited elevated basal locomotor activity when administered clonidine.

To determine whether the stimulatory effect of clonidine on locomotor activity measured in CD-1 mice at later time intervals does represent an actual increase in the basal locomotor activity rather than a prolongation of the exploratory phase due to impaired habituation, we tested the effect of clonidine in mice already habituated to the testing environment. In CD-1 mice clonidine produced a significant increase in locomotor activity approximately 1 hr after the injection. These results suggest that the action of clondine is due to an increase in the basal locomotor activity.

These results resemble those obtained in Wistar rats, in which 0.1–0.8 mg/kg clonidine was found to elevate basal locomotor activity but depressed exploratory activity [5,6]. In experiments on L-dopa-induced hypermotility clonidine apparently inhibited only that phase of hyperactivity which was associated with a rise in cerebral norepinephrine concentrations, but not that which depended on an increased activation of the dopaminergic receptor [5,6].

The late increase in locomotor activity might be brought about by a relative predominance of the dopaminergic system over the noradrenergic one in the brain. Clonidine does not inhibit the dopaminergic receptor [1] but it does potentiate a stereotyped response to the dopaminergic stimulation as do central alpha-noradrenergic blocking agents [25].

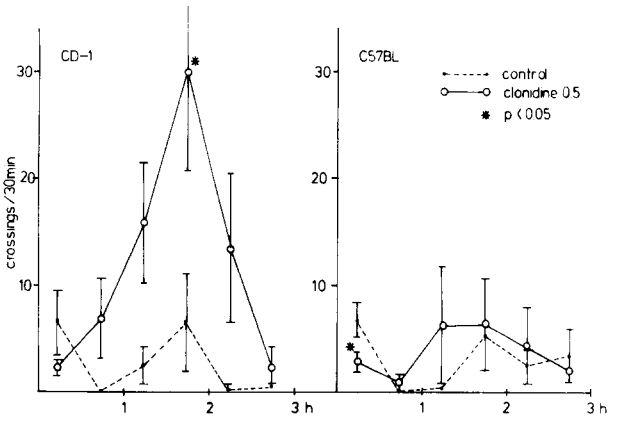

FIG. 8. The effect of 0.5 mg/kg clonidine on the changes in locomotor activity of CD-1 and C57BL/6 mice which were previously habituated to the actometer. The animals were kept in the actometer for at least 60 min before treatment and were injected with clonidine or saline at time 0. Each point represents the mean (± SEM) of 8 results.

However, in view of seemingly low reactivity of CD-1 mice to catecholaminergic stimulation, such an explanation appears unlikely. It might be suggested that the late increase in locomotor activity is due to clonidine inhibition of the serotonergic system. Clonidine exhibits antiserotonin activity, assessed by inhibition of head twitches induced by serotonergic agents [7]. The possible antiserotonergic action of clonidine has been considered responsible for its potentiation of apomorphine hypermotility [23].

The exploratory activity of C57BL/6 mice was stimulated by amphetamine, although the lower dose of 1 mg/kg produced a bimodal pattern of response. This is similar to effects observed in Wistar rats [5]. In CD-1 mice 2 mg/kg amphetamine did not significantly change the locomotor activity. However, the 1 mg/kg dose did produce an inhibition of exploration in a large proportion of CD-1 mice. The mechanism of this inhibitory action of amphetamine is not clear but might result from a secondary stimulation of the serotonergic system subsequent to activation of the dopamine receptor [22].

The interaction between clonidine and amphetamine indicated that at these doses amphetamine is unable to alter clonidine effects in either strain of mice. If most actions of clonidine have been attributed to inhibition of the central noradrenergic transmission via stimulation of presynaptic alpha-adrenoceptors [36], the presynaptic action of clonidine might abolish the presynaptic effects of amphetamine.

The central dopaminergic system of C57BL/6 mice is highly sensitive to dopaminergic stimulation [38]. Since exploratory locomotor activity might depend on the activity of the noradrenergic system, it might be concluded from our results that this system is also very sensitive in C57BL/6 mice. Also, since CD-1 mice are resistant to the action of compounds stimulating or disrupting transmission in the noradrenergic system, the change in exploratory activity may be regarded as an index of the drug action.

The increase in the basal locomotor activity due to clonidine was observed only in CD-1 mice. The reason for this difference between CD-1 and C57BL/6 mice is presently not known. It seems that some explanation may be given by experiments in which the responses of mice in these two strains to central serotoninomimetics would be compared.

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