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A Rapid and Simple Behavioural Screening Method for Simultaneous Assessment of Limbic and Striatal Blocking Effects of Neuroleptic Drugs

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LJUNGBERG, T. AND U. UNGERSTEDT. *A rapid and simple behavioural screening method for simultaneous assessment of limbic and striatal blocking effects of neuroleptic drugs.* PHARMACOL BIOCHEM BEHAV **23**(3) 479–485, 1985.—A simple and rapid screening method, where the ability of neuroleptic drugs to antagonise the abnormal pattern of exploration induced by a low dose of d-amphetamine in a 10 min test, was evaluated. The d-amphetamine 2 mg/kg pretreatment induced both an increased locomotion, thought to reflect an increased dopamine transmission in the nucleus accumbens, and weak stereotypies, thought to reflect an increased dopamine transmission in the neostriatum. Haloperidol, chlorpromazine and thioridazine blocked all ongoing behaviours while clozapine and sulpiride, regarded as causing less extrapyramidal side effects in the clinic, only antagonised the d-amphetamine induced locomotion. The findings support the notion that the common site of action for anti-psychotic drugs is blockade of dopamine receptors outside the neostriatum while the blockade of dopamine receptors within the striatum probably are related to the propensity of these drugs to induce the extrapyramidal side effects. It seems possible with this method to screen neuroleptic drugs for their relative potency in blocking limbic and striatal dopamine receptors simultaneously in one short experiment. The method might be used when new anti-psychotic drugs with low incidences of extrapyramidal side effects are sought for.

Neuroleptics Amphetamine Stereotyped behaviours Locomotion Screening test Holeboard

THE anti-psychotic effect of neuroleptic drugs are thought to be due to their ability to block dopamine 2 (D2) receptors in the brain [5, 29, 32]. However, not only the anti-psychotic effect but also some severe and unwanted side effects, e.g., acute dystonia, Parkinsonism and tardiv dyskinesias, are related to an unselective D2 receptor blockade in the brain (see e.g. [31,32]). According to the current most accepted view, the anti-psychotic effect may be due to a blockade of dopamine receptors in limbic/cortical areas while the extrapyramidal side effects are caused by a dopamine receptor blockade in the neostriatum [21, 30, 31]. The development of new anti-psychotic drugs with a more selective action in the limbic system might be one strategy to handle the problem with the severe extrapyramidal side effects.

When dopamine transmission is artificially increased in animals, by treating them with dopamine agonistic drugs, a variety of abnormal and stereotyped hyperkinetic movements and behavioural patterns are induced. Antagonism of these various abnormal movements is the most used behavioural method in screening experiments to find new dopamine receptor blockers, which could potentially be used as new anti-psychotic drugs [12, 13, 23, 34].

Initially most interest was focused on the ability of neuroleptic drugs to antagonise the so called "stereotyped behaviours," like sniffing, repetitive head and forelimb movements and licking, biting and compulsing gnawing, induced by dopamine agonists like d-amphetamine and apomorphine. However subsequent research has found that this action is probably related to striatal dopamine mechanisms and therefore more related to the propensity of neuroleptic drugs to induce the unwanted extrapyramidal side effects than their beneficial antipsychotic effect [5, 7, 8, 9, 12, 22, 27]. It was also found that some neuroleptic drugs with documented anti-psychotic effects in the clinic, like clozapine and sulpride, were not very effective antagonising stereotyped behaviours induced by an increased dopamine transmission [3, 9, 10, 14, 17, 19, 20, 23, 28, 33, 34, 35]. These drugs also show a low tendency to induce extrapyramidal side effects in the clinic [1,24].

The finding that locomotion could be induced by an increased dopamine transmission in a limbic area, e.g., the nucleus accumbens septi [11,26], gave the ability to develop a new behavioural screening method where the effect on limbic dopamine receptors could be assessed separately. It has been found that all anti-psychotic drugs are effective in antagonizing the locomotion induced by an increased dopaminergic transmission, even clozapine and sulpiride [4, 9, 11, 18, 19, 25, 28, 34, 35].

Based on these results it would therefore be of great interest to develop a rapid and simple behavioural screening

method where the antagonistic effect of new potential antipsychotic drugs could be simultaneously assessed on the locomotion induced by an increased dopamine transmission in limbic *and* on the stereotyped behaviour induced by an increased dopamine transmission in the neostriatum.

In this paper we present such a model. The model is based on an automatic recording technique, the so called "hole-board apparatus" [18] and the ability of five clinically used neuroleptic drugs to antagonise the abnormal behaviours induced by d-amphetamine. The dose of d-amphetamine, and the time point of testing, is chosen so that the animals show increased locomotion, which have been related to an increased dopaminergic transmission in the nucleus accumbens [15, 16, 25], and stereotypies, related to the dopamine releasing effect of d-amphetamine in the neostriatum [5, 7, 8, 22, 27].

METHOD

The experiments were performed on 170 male Sprague-Dawley rats (ALAB, Stockholm) with a body weight of 160–210 g. The animals arrived at the animal colony at least 3 days prior to the testings and were kept 5/cage under constant temperature and humidity conditions on a 12 hour light-/dark cycle (6 a.m.–6 p.m.) with food and water ad lib. Four hours before the experiments the animals were placed individually in ordinary rat cages and moved to the weakly illuminated experimental room. After the 4 hours settling down period the animals were carefully transferred to the test box (see below) and, during 10 minutes, the reaction to the new environment was studied. All animals were used only once.

Apparatus

The behaviour of the animals was recorded in a test box designed for the automatic recording of seven components of behaviour [18]. It consisted of a modified open field (69×69 cm, with 25 cm high walls) where the animals could move around freely in the periphery but were unable to cross the middle part of the area (see Fig. 1). The movements of the animal were detected by interruptions of ten photobeams using visible light symmetrically covering the open field area. *Activity* was defined as the number of interruptions of these ten photobeams. By feeding the photobeam interruptions into a digital logic, locomotion of the animal in the open field area could also be recorded and separated from repetitive interruptions of one photobeam. *Total locomotion* was defined as the number of times the animal walked a fixed distance which was slightly less than the length of the side of the box and defined by the arrangement of the photocells. *Forward locomotion* was defined as the number of times the animal walked the same distance but continued from one arm into the next arm (see Fig. 1). Thirty-two holes (2.5 cm in diameter) were symmetrically distributed over the entire floor. Six photobeams, one for each row of holes, were mounted under the floor in such a way that a beam was interrupted as soon as the nose of the animal was lowered deeper than 0.5 cm into a hole as measured from the surface of the floor. *Hole count* was defined as the number of interruptions of these photobeams and *hole time* was the accumulated time the photobeams were interrupted. One photobeam directed vertically was positioned in each corner. *Corner count* was defined as the number of interruptions of these photobeams and *corner time* was the accumulated time these photobeams were interrupted. The hole-board itself was placed in an outer sound protecting box (1×1×1 m) with a small Plexiglas observation window at the top. An electric fan ventilated the box at the same time as it provided a constant background noise. The assembly was placed in a weakly illuminated room.

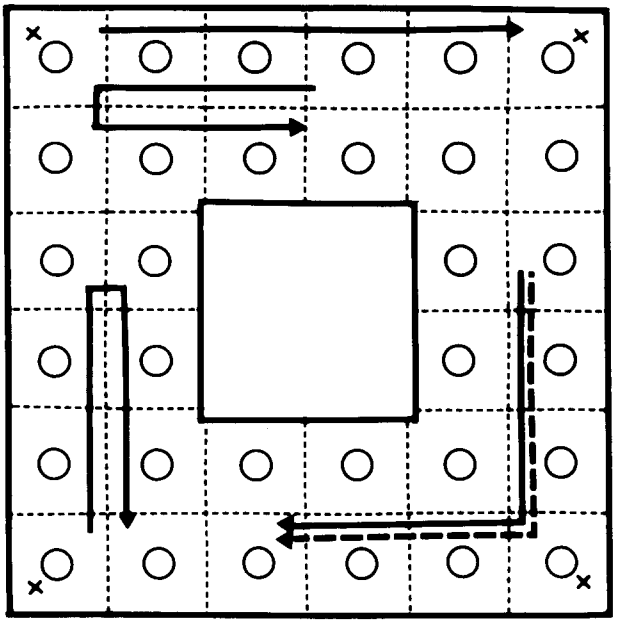

FIG. 1. The testbox consists of a modified open-field symmetrically covered by ten photobeams (thin dotted lines). *Activity* is number of interruptions of these photobeams. A *locomotion* count is obtained every time the animals walk a fixed distance defined by programming of the photobeams. A *total locomotion* count corresponds to the distance walked by the animal as shown by the solid lines and a *forward locomotion* count corresponds to the distance walked by the animal as shown by the thick dotted line. The "X" in the corners shows position of vertical photobeams detecting entries of animal into corner. *Corner count* is number of interruptions of these photobeams and *corner time* is accumulated time of interruption. Thirty-two holes are distributed over the floor. Photobeams are mounted under the floor to detect when animal lowers its head into hole. *Hole count* is number of interruptions of these photobeams and *hole time* is accumulated time of interruption.

All the data from the test box were fed on-line into a WANG 2200-S minicomputer for statistical analysis and group comparisons.

Concomitant with the automatic recordings more than $^2/_3$ of the animals were also observed and notes with a description of the behaviour were taken and compared with the automatic recordings. For a further description of this technique see Ljungberg and Ungerstedt [18].

Drug Treatments

D-amphetamine-sulfate and thioridazine-HCl (Sandoz) were dissolved in isotonic saline and the doses refer to the bases. Clozapine (Sandoz) was dissolved in a minimal quantity of 1 M HCl-acid and made up to volume with isotonic saline. Haloperidol (Haldol, Leo), chlorpromazine (Hibernal, Leo) and sulpiride (Equilid, Lepetit) were obtained as commercially available injection ampoules and were diluted to volume with isotonic saline. The doses refer to the above mentioned form. All injections were given intraperitoneally

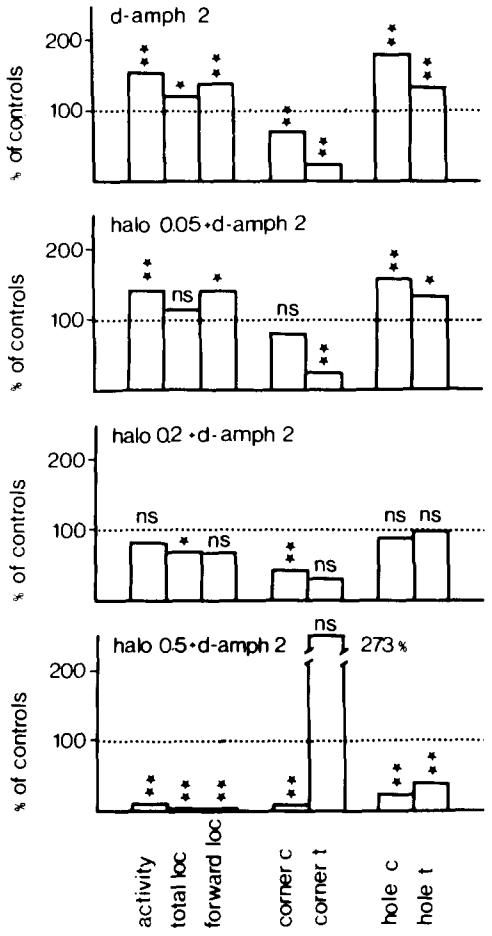

FIG. 2. Haloperidol was given 80 minutes and d-amphetamine 50 minutes before the animals were placed in the testbox and the behaviour of the animals was recorded during their initial ten minutes in the box. The figure shows the group median values for the haloperidol+d-amphetamine treated animals compared to the saline injected controls (=100%). (Haloperidol 0.05 mg/kg: n=6, 0.2 mg/kg: n=6, 0.5 mg/kg: n=6.) (*$p<0.05$ and **$p<0.01$.)

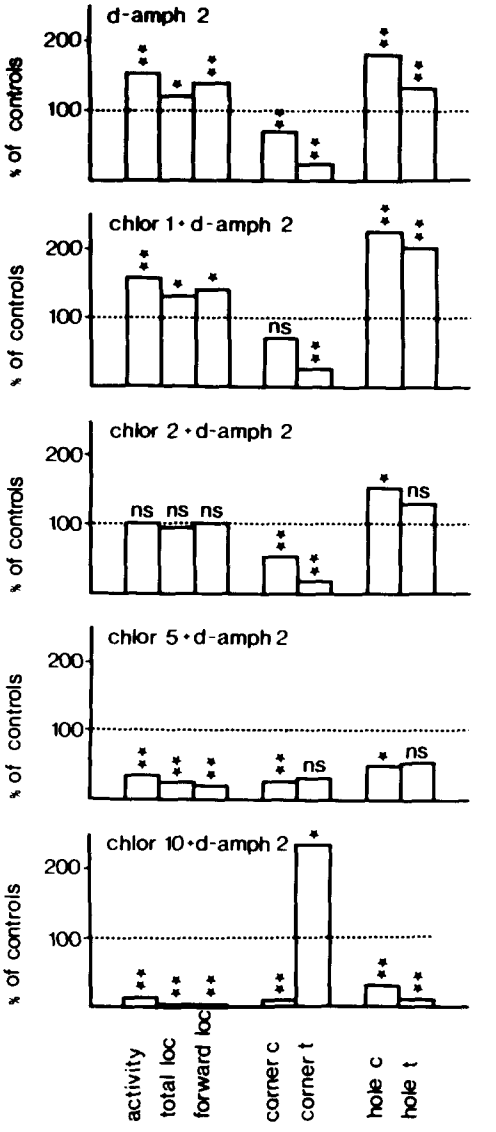

FIG. 3. Chlorpromazine was given 80 minutes and d-amphetamine 50 minutes before the animals were placed in the testbox and the behaviour of the animals was recorded during their initial ten minutes in the box. The figure shows the group median values for the chlorpromazine+d-amphetamine treated animals compared to the saline injected controls (=100%). (Chlorpromazime 1 mg/kg: n=6, 2 mg/kg: n=6, 5 mg/kg: n=6, 10 mg/kg: n=4.) (*$p<0.05$ and **$p<0.01$.)

in a volume of 5 ml/kg body weight. The d-amphetamine and saline injections were given 50 minutes and the pretreatments 80 minutes before the 10 minutes test period.

Statistics

The medians were calculated for all groups and in the following data are presented as percent of controls. The Mann-Whitney U-test was used for calculations of the degree of significance (Siegel, 1956) (*$p<0.05$, **$p<0.01$).

RESULTS

Controls

The controls showed intense exploratory behaviour during the 10 minute test period. It consisted of varied locomotion in the test box mainly along the outer walls with relatively few attempts to explore the area around the cube in the middle. This behaviour was accompanied by sniffing, some rearing and head dippings into the holes. The absolute number of counts obtained in the automated recordings for the controls were: *activity:* 532, *total locomotion:* 54, *forward locomotion:* 36, *corner counts:* 71, *corner time:* 128, *hole counts:* 91, *hole time:* 76 (n=13).

D-amphetamine

D-amphetamine 2 mg/kg (see Figs. 2–6) caused an increase in the recorded locomotion. This locomotion was more automatic and less varied, which is reflected in a greater increase in *forward locomotion* as compared to the increase in *total locomotion* (*forward locomotion/total locomotion*=0.67 for controls and 0.79 for d-amphetamine 2

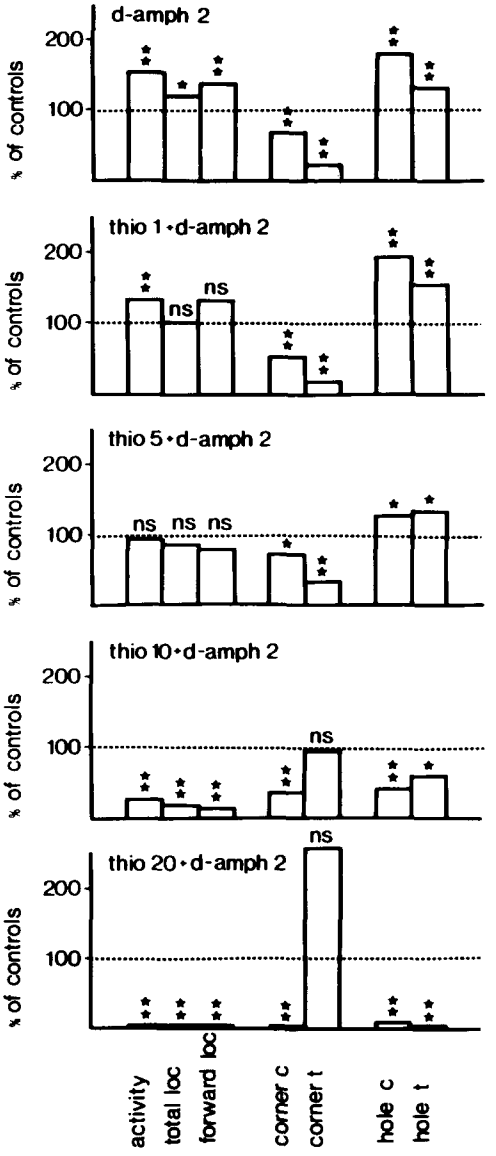

FIG. 4. Thioridazine was given 80 minutes and d-amphetamine 50 minutes before the animals were placed in the testbox and the behaviour of the animals was recorded during their initial ten minutes in the box. The figure shows the group median values for the thioridazine+d-amphetamine treated animals compared to the saline injected controls (=100%). (Thioridazine 1 mg/kg: n=6, 5 mg/kg: n=6, 10 mg/kg: n=6, 20 mg/kg: n=6.) (*$p<0.05$ and **$p<0.01$.)

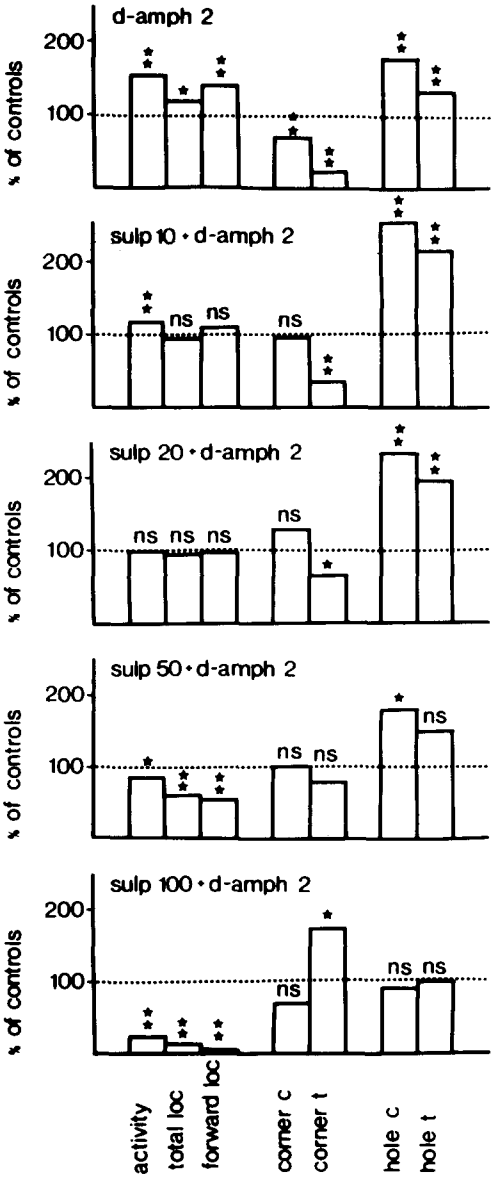

FIG. 5. Sulpiride was given 80 minutes and d-amphetamine 50 minutes before the animals were placed in the testbox and the behaviour of the animals was recorded during their initial ten minutes in the box. The figure shows the group median values for the sulpiride+d-amphetamine treated animals compared to the saline injected controls (=100%). (Sulpiride 10 mg/kg: n=6, 20 mg/kg: n=6, 50 mg/kg: n=6, 100 mg/kg: n=6.) (*$p<0.05$ and **$p<0.01$.)

mg/kg, $p<0.01$). The animals also showed an increase in sniffing and rearing and made more head dips into the holes. The position of the animals in the test box was also changed and the animals were more active in the middle of the open field area with sniffing and rearing also in the vicinity of the cube in the middle, thereby causing a decrease in both recorded *corner count* and *corner time* as compared to the controls. D-amphetamine 2 mg/kg induced weak stereotypies mainly consisting of sniffing and repetitive head and forelimb movements.

D-amphetamine 1 mg/kg induced principally the same changes but the effect was not as pronounced. After d-amphetamine 4 mg/kg the animals showed a more intense stereotype behaviour with intense sniffing on the floor, repetitive head and forelimb movements and some licking, biting and gnawing (the recordings of gnawing are not included in the present papers). The locomotion was decreased as compared to d-amphetamine 2 mg/kg and with the development of more severe stereotypies there was a decrease in the head dips into the holes. The absolute number of counts obtained in the automated recordings for the d-amphetamine 1 (n=6) and 4 (n=6) mg/kg treated animals were: *activity:* 655, 649 (**, **); *total locomotion:* 56, 53 (n.s.); *forward locomotion:* 43, 32 (n.s.); *corner counts:* 51, 66 (n.s.); *corner time:* 29, 28 (**, **); *hole counts:* 144, 121 (**, n.s.); *hole time:* 85, 56 (n.s.).

Haloperidol, Chlorpromazine and Thioridazine

As the results obtained for haloperidol, chlorpromazine and thioridazine were principally the same, the results are described together. All three drugs blocked in a dose related manner the *activity* and *locomotion* and, with somewhat lesser potency, the head dips into the holes in the d-amphetamine treated animals. None of these drugs could reverse the d-amphetamine induced change of the position of the animals in the test box, i.e., the animals still remained more out in the open field area except after the highest doses tested when all ongoing behaviour was blocked and the animals were lying inactive in the corners (see Figs. 2–4).

Sulpiride

Sulpiride antagonised in a dose related manner the *activity* and *locomotion* in the d-amphetamine treated animals. The position of the animals was markedly affected by the sulpiride pretreatment and the animals were less often active out in the open field but instead, like the controls, in the vicinity of the outer walls and in the corners (seen as an increase in *corner count* and *corner time*). The stereotypies induced by d-amphetamine were not antagonised by sulpiride, not even after a dose of 100 mg/kg. The stereotyped up and down movements of the heads were more often directed into the holes (see Fig. 5).

Clozapine

Clozapine antagonised in a dose related manner the head dips into the holes after d-amphetamine. Clozapine 5 mg/kg reduced the *activity* and *locomotion* to control values while at the same time increased the *corner count* and *corner time*, i.e., it changed the position of the animals back to being more active in the periphery of the testbox. At this dose the animals still showed piloerection and some stereotyped movements of the head. After 15 mg/kg there was a more stereotyped, non-varied, locomotion (increase in *forward locomotion*) and more repetitive head movements. After the highest dose tested (30 mg/kg) the animals still showed some of this non-varied locomotion along the side walls of the cage. When not locomoting the animals were sitting in the corners showing stereotyped repetitive head movements (see Fig. 6).

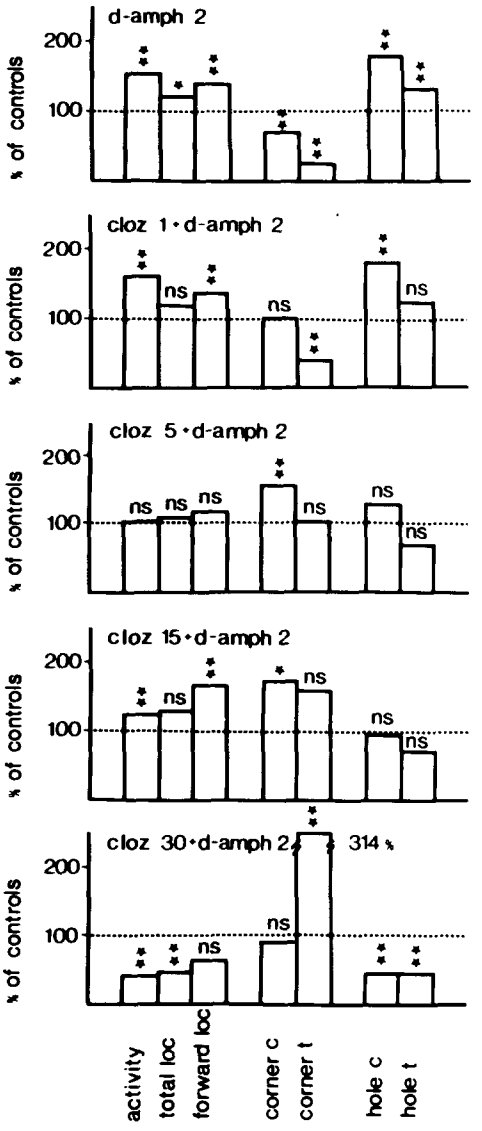

FIG. 6. Clozapine was given 80 minutes and d-amphetamine 50 minutes before the animals were placed in the testbox and the behaviour of the animals was recorded during their initial ten minutes in the box. The figure shows the group median values for the clozapine+d-amphetamine treated animals compared to the saline injected controls (=100%). (Clozapine 1 mg/kg: n=7, 5 mg/kg: n=6, 15 mg/kg: n=6, 30 mg/kg, n=6.) (*$p<0.05$ and **$p<0.01$.)

DISCUSSION

In the present study d-amphetamine 2 mg/kg induced an abnormal pattern of exploration which included both aspects of stereotyped behaviours and an increased locomotion. These two different patterns of abnormal behaviours induced by d-amphetamine have previously been related to an increased dopaminergic transmission in the neostriatum and nucleus accumbens respectively (see introduction).

Haloperidol and chlorpromazine antagonised in a dose dependent manner d-amphetamine induced stereotypies while both clozapine and sulpiride failed to do so. It even seemed as if clozapine and sulpiride even increased the stereotypies induced by the d-amphetamine. These results are in good agreement with previous descriptions in the literature [3, 9, 10, 13, 14, 17, 20, 23, 28, 33, 34, 35]. All of the tested drugs could antagonise the d-amphetamine induced locomotion. This also agrees well with previous reports [11, 20, 25, 28] and support the notion that the common site of actions of anti-psychotic drugs is their ability to block dopamine receptors in the limbic system [21, 30, 31].

In previous publications the effects of thioridazine on d-amphetamine induced behaviour have not been totally consistent. Thioridazine has for example been claimed to antagonise [3,20], not to antagonise [13] or to increase the d-amphetamine induced stereotypies [28]. In the present study thioridazine could antagonise the weak stereotyped movements induced by the low dose of d-amphetamine. Thioridazine has previously been described to antagonise the locomotion induced by systemic injections of

d-amphetamine [20,28], apomorphine [9, 19, 34, 35], L-DOPA [20] or the locomotion induced by dopamine applied locally into the nucleus accumbens [4]. These results are in good agreement with our results. Thioridazine has, however, also been reported not to antagonise the apomorphine [20] or the d-amphetamine induced locomotion [2]. These inconsistencies of the effects of thioridazine in the literature might depend on the dose of d-amphetamine used, the time point of testing, the injection routes or the method of recording used.

In the present study both clozapine and sulpiride could antagonize the d-amphetamine induced locomotion more potently than the d-amphetamine induced stereotypies while haloperidol, chlorpromazine and thioridazine antagonised all aspects of d-amphetamine induced behaviours. As chlorpromazine, thioridazine and clozapine are potent alpha adrenergic and muscarinic receptor blockers while haloperidol and sulpiride are not, this difference in antagonistic properties cannot only be explained by any additional effects on these receptors (for references see e.g., [9, 19, 35]).

In summary it therefore seems as if this simple screening test, where the antagonistic properties of neuroleptic drugs are tested against an abnormal pattern of exploration induced by a low dose of d-amphetamine can detect, and simultaneously assess, in a short time period, effects on limbic and striatal dopamine mechanisms separately. This method might therefore be used in screening experiments where new possible anti-psychotic drugs with low incidences of extrapyramidal side effects are sought for.

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