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Antiapomorphine and Locomotor Effects of Neuroleptics in Rhesus Monkeys

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PORSOLT, R. D., S. ROUX AND M. JALFRE. *Antiapomorphine and locomotor effects of neuroleptics in rhesus monkeys.* PHARMAC. BIOCHEM. BEHAV. 17(6) 1309–1312, 1982.—Intramuscular injections of apomorphine (1 mg/kg) cause marked behavioral effects in rhesus monkeys including hyperactivity, repetitive stereotyped movements, chewing, tongue movements, licking, biting and vocalizatioon. These effects occur within minutes of the injection and last 90–100 min. The antiapomorphine and locomotor depressant activity of chlorpromazine, haloperidol, MD 790501, sultopride and thioridazine, injected IM 1 hr before apomorphine, were assessed using a standardized rating procedure. All compounds antagonized the effects of apomorphine but differed in terms of potency and their relative effects on locomotor activity. The experimental compound MD 790501, a new benzamide derivative, was not only the most potent compound tested but, compared with its antagonism of apomorphine, caused the least marked depression of locomotor activity.

Apomorphine antagonism Rhesus monkey Neuroleptics Phenothiazines Butyrophenones Benzamides MD 790501

THE principal pharmacological activity of neuroleptics is their antagonism of the various kinds of stereotyped behavior induced by dopamine (DA) stimulants [2,6]. Generally these tests are performed in mice and rats and very little work has been reported in monkeys [1, 6, 7]. Although research with monkeys is more time consuming and expensive than with rodents, the greater proximity of primates to man should increase the reliability of extrapolations from this species in particular for predicting clinically effective doses. We report here a procedure in rhesus monkeys for assessing both the antiapomorphine and locomotor depressant effects of neuroleptics in the same animal at the same time. The results indicate that different neuroleptics can be differentiated in terms of these two parameters in a manner which may be useful for characterizing their clinical profile of activity.

METHOD

Animals

Eight rhesus monkeys (7 females and 1 male) weighing 5.5–8 kg were used. They were singly housed in stainless steel squeeze-back cages (58×85×67 cm) and were fed once daily at 4–30 p.m. on a diet consisting of standard monkey pellets supplemented with fresh fruit. The animal room was temperature controlled at 22°C and was maintained on a 12 hr light-dark cycle which commenced at 7 a.m.

Drugs

The following drugs were used: apomorphine HCl (injectable ampoules), chlorpromazine HCl, haloperidol (injectable ampoules of HALDOL), MD 790501 ([exo]-2,3-dimethoxy-N-[8-(phenylmethyl)-8-aza-bicyclo[3.2.1.]oct-3-yl] benzamide, HCl), sultopride HCl and thioridazine HCl. The drugs were dissolved or diluted in distilled water and were administered IM in a volume of 0.5 ml/kg, doses being expressed in terms of the salt or base where appropriate.

Procedure

All injections and observations were performed with the animals in their home cages. The neuroleptics were injected IM at 9 a.m. and 1 hr later the animals received an IM injection of 1 mg/kg apomorphine. To determine the initial effects of the neuroleptics the animals were observed for the presence (1) or absence (0) of hypoactivity immediately before injection of apomorphine. They were then observed for the presence of apomorphine effects and hypoactivity 8 times over a 2 hr period. Observations, which each lasted 5 minutes, started 15 minutes after the injection of apomorphine and were repeated at 15 minute intervals until 2 hr after the injection of apomorphine. Apomorphine effects were assessed by noting the presence (1) or absence (0) of each of the 8 following symptoms: hyperactivity, aggressiveness, repetitive stereotyped movements, chewing, tongue movements, licking, biting and vocalization. The maximal possible score for apomorphine effects was thus 8 per observation and 64 for the experimental period (8 observations). The presence (1) or absence (0) of hypoactivity was noted at each observation giving a maximal hypoactivity score of 8 for the experimental period.

Four animals (from the pool of 8) were tested per compound with each animal receiving each dose or the vehicle in a counterbalanced order. There were at least 3 days between injections to avoid residual effects. All observations were performed "blind" by the same observer (S.R.).

The antiapomorphine activity of the compounds was es-

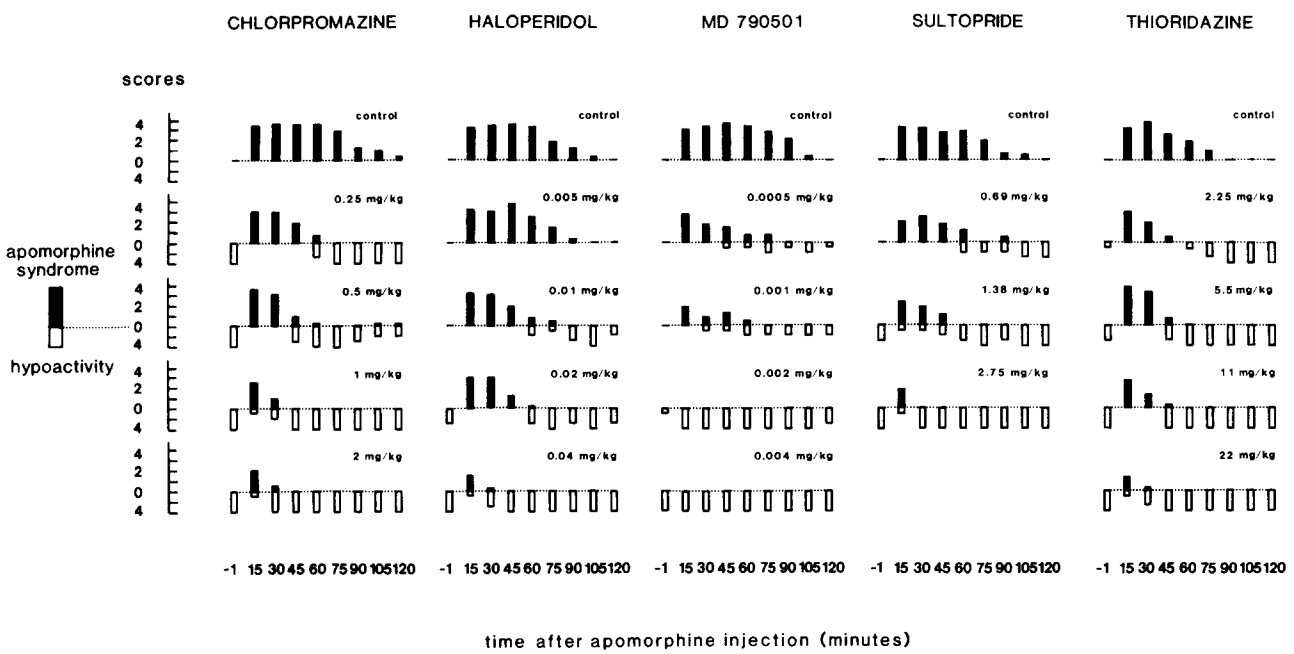

FIG. 1. Antiapomorphine effects (black columns) and locomotor depressant effects (white columns) of 5 different neuroleptics administered IM 1 hr before apomorphine (1 mg/kg). Apomorphine score: mean number of apomorphine-induced symptoms present at each observation time (maximum 8). Hypoactivity score: number of animals displaying hypoactivity at each observation time (maximum 4).

timated from the dose, calculated by regression analysis, which decreased the apomorphine score by 50% (ID 50). The locomotor depressant effect of the compounds was estimated from the dose, calculated by regression analysis, which caused a half maximal hypoactivity score (ID 50).

RESULTS

Effects of Apomorphine Alone

Intramuscular injection of apomorphine alone (1 mg/kg) had marked effects on the behavior of all the monkeys we have tested but with a different pattern of response between animals. All monkeys displayed a marked hyperactivity accompanied by repetitive stereotyped movements usually of the whole body but sometimes only of one part, in particular the head. The hyperactivity often occurred together with persistent chewing and tongue movements. In some animals apomorphine induced a kind of aggressive behavior where the animals appeared to threaten either the observer or parts of their cage and vocalized in the form of barking or grunting. Other animals were observed to lick either themselves or the cage in a highly repetitive manner. In one of these animals the stereotyped hand licking observed after each injection of apomorphine progressed on one occasion to self gnawing resulting in such injury to its hand that the animal had to be withdrawn from the experiments. Apomorphine caused cage biting in several animals and in one of them frequently induced a frenzied behavior where the animal compulsively attacked the bars of its cage and appeared to lose all responses to environmental stimuli. Sniffing, as seen in rodents, was never observed. In general, despite these marked and sometimes dramatic behavioral effects, it is of interest to note that on no occasion did apomorphine induce vomiting even in animals where spontaneous vomiting sometimes occurs. Despite the marked differences between monkeys in their response to apomorphine, the individual patterns were highly reproducible from one occasion to another.

Antiapomorphine Effects of Different Neuroleptics

All the neuroleptics tested antagonized apomorphine-induced behavioral effects in a dose-dependent manner but differed markedly in their potency (Fig. 1 and Table 1). The most potent compound tested was the new benzamide derivative, MD 790501, which was about 40 times more potent than haloperidol and 700 times more potent than chlorpromazine. The antagonism of apomorphine by neuroleptics in these experiments can best be described as a decrease in the breakthrough effect of apomorphine against a neuroleptic background usually but not necessarily indicated by the presence of hypoactivity. Inspection of Fig. 1 suggests that neuroleptics reduced the duration of the apomorphine breakthrough rather than its amplitude as measured by the number of symptoms present.

All compounds caused dose-dependent hypoactivity at doses close to those which antagonized the effects of apomorphine, although hypoactivity in any one animal never coexisted with signs of apomorphine stimulation. The compounds could, however, be differentiated by comparing their antiapomorphine activity with their locomotor depressant effects. For example, MD 790501 at 0.0005 and 0.001 mg/kg strongly attenuated the effects of apomorphine without causing marked hypoactivity. Even at 0.002 mg/kg, a dose which entirely suppressed the effects of apomorphine, the hypoactivity scores at the beginning and the end of the experimental period were less than maximal. In contrast chlorpromazine, even at the lowest dose tested, caused pronounced hypoactivity 1 hr after injection, which disappeared as apomorphine

TABLE 1

ANTIAPOMORPHINE AND LOCOMOTOR DEPRESSANT EFFECTS OF DIFFERENT NEUROLEPTICS

Drug	ID_{50} (mg/kg IM) (95% Confidence Limits) Antiapomorphine	ID_{50} (mg/kg IM) (95% Confidence Limits) Hypoactivity	$\frac{ID_{50}\ Hypoactivity}{ID_{50}\ Antiapomorphine}$
Chlorpromazine	0.28 (0.11–0.68)	0.24 (0.08–0.74)	0.85
Haloperidol	0.015 (0.006–0.036)	0.016 (0.009–0.028)	1.07
MD 790501	0.00037 (0.00018–0.00078)	0.00096 (0.00033–0.0028)	2.59
Sultopride	0.75 (0.69–0.81)	0.90 (0.20–4.04)	1.20
Thioridazine	5.09 (0.3–88)	3.37 (1.32–8.63)	0.66

took effect, to reappear 60 minutes later as the apomorphine effect subsided. Even at the highest dose of chlorpromazine (2 mg/kg), which caused marked hypoactivity lasting over 8 hr, a clear effect of apomorphine was apparent 15 minutes after apomorphine injection. Thioridazine had a profile of activity similar to chlorpromazine whereas the results obtained with haloperidol and sultopride were intermediate between the two phenothiazines and MD 790501. These differences are reflected in the ID 50 measures (Table 1). The ID 50's for the antiapomorphine activity of chlorpromazine and thioridazine were higher than their ID 50's for hypoactivity, whereas the antiapomorphine ID 50 for MD 790501 was about 2.5 times lower than its ID 50 for hypoactivity. With haloperidol and sultopride the dose ratios ID 50 hypoactivity/ID 50 antiapomorphine were intermediate.

DISCUSSION

The present experiments have shown that a marked and characteristic syndrome can be induced in rhesus monkeys by IM injections of apomorphine. The behavior observed appears to be qualitatively similar to that described in the cynomolgus macaque [7] and in the cercopithecus monkey [1], occurs at similar doses (1 mg/kg) and has a similar time course (90–110 minutes). Furthermore the patterns of apomorphine-induced behavior appear to be similar to those induced by amphetamine or methamphetamine [6]. Apomorphine-induced behavior in monkeys appears to differ, however, from that observed in rodents where the symptoms tend to occur in a more hierarchical order of intensity depending on the dose, starting with sniffing and ending with compulsive gnawing [2]. In monkeys the pattern of effects, although highly reproducible, is much more variable from one animal to another and it is thus difficult to assign individual symptoms to a hierarchy of intensity valid for all animals. For this reason we chose to use a scaling system simpler than that habitually used for scoring rodent behavior [2] by assigning one point for one sign. The results obtained would seem to justify this choice in that clear and dose-dependent antagonism of the effects of apomorphine were observed with all the neuroleptics under rigorously blind conditions.

Two prominent effects of neuroleptics in animals are sedation and catalepsy. Our measure of hypoactivity does not permit a distinction between these two effects because our passive observation procedure precluded interfering with the animals during the experimental period. Subjective assessment of the animals' behavior, however, suggested that the hypoactivity observed with chlorpromazine and thioridazine was mainly due to sedation and drowsiness whereas motor rigidity appeared to contribute largely to the hypoactivity observed with haloperidol and the two benzamides, sultopride and the experimental compound MD 790501. This impression coincides with the known clinical profiles of the reference compounds [3] and concords with their propensity to induce extrapyramidal reactions in neuroleptic primed monkeys [5]. Whatever the contribution of sedation and catalepsy to the hypoactivity scores, the results obtained clearly suggest that some of the compounds, in particular MD 790501, antagonized the effects of apomorphine at doses lower than those which induced pronounced locomotor depression. The results obtained with MD 790501 confirm other pharmacological findings [4] which suggest that this chemically novel benzamide would possess highly potent antipsychotic properties in man without marked sedative or motor depressant effects.

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