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Effects of Neuroleptic Drugs on the Inhibition of Exploratory Behaviour Induced by a Low Dose of Apomorphine: Implications for the Identity of Dopamine Receptors

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STÅHLE, L. AND U. UNGERSTEDT. *Effects of neuroleptic drugs on the inhibition of exploratory behaviour induced by a low dose of apomorphine: Implications for the identity of dopamine receptors.* PHARMACOL BIOCHEM BEHAV **25**(2) 473–480, 1986.—Apomorphine in low doses inhibits spontaneous exploratory behaviour in rats. This effect is commonly referred to as an expression of selective stimulation of dopaminergic autoreceptors. The aim of the present study was to investigate the influence of neuroleptic drugs with different pharmacological profiles on this apomorphine induced inhibition of exploration using techniques for detailed recording of behaviour and multivariate statistical analysis of the results. By comparison with dose response analyses of apomorphine it was possible to determine whether a neuroleptic specifically antagonised the apomorphine effect or if the pattern of behaviour was qualitatively changed in some way. Apomorphine (0.05 mg/kg) was tested against cis-flupenthixol (0.01–0.5 mg/kg), haloperidol (0.01–0.1 mg/kg), metoclopramide (0.2–5 mg–kg), sulpiride (0.5–50 mg/kg) and SCH 23390 (0.005–0.05 mg/kg). Metoclopramide and haloperidol had weak antagonising effects against apomorphine while cis-flupenthixol and SCH 23390 was completely inefficient in this respect. The multivariate analysis indicated that the effects of haloperidol was restricted to only some aspects of the behavioural effects of apomorphine. Only sulpiride did selectively and dose-dependently antagonise the apomorphine induced behavioural suppression. The data provide evidence for a functional subdivision of dopamine receptors at the behavioural level.

Apomorphine Autoreceptor Behaviour Cis-flupenthixol Dopamine Haloperidol Holeboard Metoclopramide Principal components SCH 23390 Sulpiride

IT is well known that low doses of the dopamine agonist apomorphine (APO) inhibits spontaneous or exploratory behaviour in rodents [18, 25, 33]. Commonly this effect is attributed to stimulation of dopaminergic autoreceptors [4]. These autoreceptors are more sensitive than postsynaptic receptors to dopamine agonists such as APO [26]. In the low dose range APO decreases firing of dopamine neurons [1], inhibits dopamine synthesis by lowering the activity of tyrosine hydroxylase [33,38] and reduces dopamine release *in vivo* [36,42] and *in vitro* [8, 31, 39]. It has been reported that low doses of APO "paradoxically" improve patients with dyskinetic disorders such as Huntingtons chorea [35] and tardive dyskinesia [5] and that APO reduces schizophrenic morbidity in some patients [6,27]. These findings make the pharmacological characterisation of the effects of low doses of APO important.

We have previously described a recording apparatus for multivariate measurement of behaviour [19,29] which allows simultaneous recording of ten variables. In this connection we have applied some multivariate statistical methods [29, 30, 40] which allows description and analysis of principal components (PCA) of the behavioural pattern. By means of PCA, the quantitative dose-response analysis can be restricted to a specific pattern of behaviour (e.g., the decrease in exploratory behaviour obtained after treatment with low doses of APO). In addition the PCA can detect qualitative changes in the pattern of behaviour caused by changing the dose of the drug (e.g., the appearance of stereotypies following higher doses of APO) [29,30]. In a previous paper these methods were used to examine the effects of various doses of APO on exploratory behaviour in rats [29]. It was then found that within a restricted dose interval (0.01–0.1 mg/kg SC) APO dose-dependently inhibits exploration without any signs of stereotyped behaviour.

In the present study we extend the use of PCA to involve agonist-antagonist interaction experiments. The effects of four neuroleptics and the D1-receptor antagonist SCH 23390 [12,13] on the inhibition of exploration induced by a low dose of APO (0.05 mg/kg) was examined. It was found that only sulpiride selectively antagonises APO.

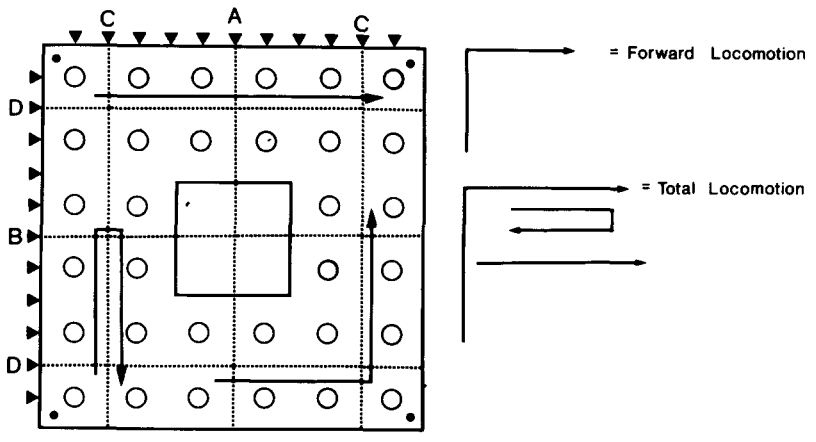

FIG. 1. The holeboard from above schematically. The black triangles indicate ACTIVITY diodes 4 cm above the floor emitting infra-red light detected on the opposite side. The arrows indicate the path animals have to move in order to reach the criteria set to get a FORWARD LOCOMOTION or a TOTAL LOCOMOTION count (also see the text). Under the floor (0.5 cm) there is a photobeam under each of the six rows of holes, detecting the HOLE variables. The CORNER variables are detected by vertical photobeams in the corners (black dots) and the REARING variables are detected by a field of photobeams 12.5 cm above the floor.

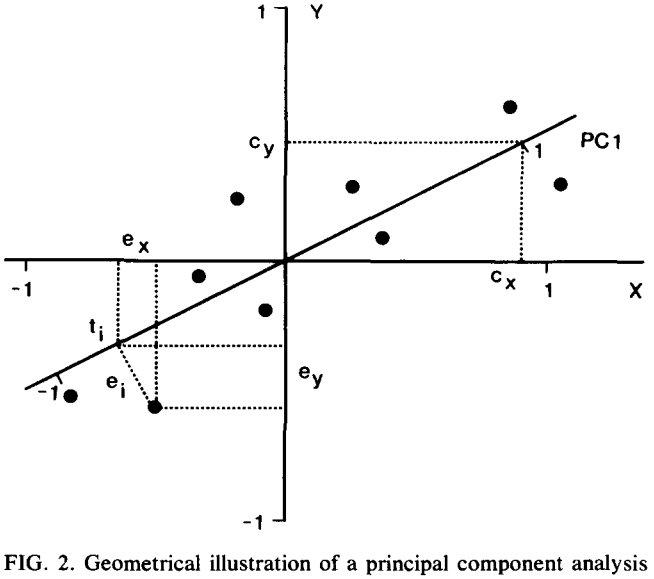

FIG. 2. Geometrical illustration of a principal component analysis (PCA) in a two-dimensional space with the original measurements X and Y (e.g., locomotion and rearing). The scales are the same on the principal component (PC1) and on X and Y. The principal component score (t-score) of each data point is its projection onto PC1. The loadings of X and Y on PC1 are the direction cosines of PC1, i.e., the projections of the t-score 1.0 onto X and Y respectively (C_x and C_y in the figure). The error of an object is e_i which may be decomposed into e_x and e_y ($e_x^2 + e_y^2 = e_i^2$). PC1 is fitted by minimising the sum of e_i^2.

METHOD

Subjects

Male Sprague-Dawley rats (Anticimex, Sweden), weighing 140–240 g, were used throughout. They were delivered to the animal department at least two days before the experiment and were housed five per cage. The animals had access to ordinary lab chow and tap water (ad lib) except during experimental procedures. They were kept on a constant 7 a.m./7 p.m. light dark schedule. Each animal was used only once.

Recording of Behaviour

An automatic holeboard, essentially similar to the one described by Ljungberg and Ungerstedt [19], was used. The apparatus consisted of an open field (70×70 cm). A transparent plastic cube in the centre of the open field restricts movements to the four arms thus formed. Thirty-two holes were evenly distributed in the floor (see Fig. 1). Three horizontal rows of photobeams allows seven different behavioural variables to be defined and quantitated. With one vertical photobeam in each corner two other variables could be detected. Impulses from the photobeams were fed into a digital logic in order to define the nine variables (see below). For more details see [19,29].

Definition of the Recorded Behavioural Variables

ACTIVITY—Interruption of any of the 22 (11 + 11) horizontally oriented photobeams (black triangles in Fig. 1) placed 4 cm above the floor gives a count. Thus horizontal movements are registered. FORWARD LOCOMOTION—Interruption of an ACTIVITY photobeam A (or B) gives a count if it is preceded by interruption of ACTIVITY photobeam B (or A) on either of the adjacent sides. This variable corresponds to the rat walking from the middle of one of the arms to the middle of the next arm (arrow in Fig. 1). TOTAL LOCOMOTION—Interruption of ACTIVITY

TABLE 1

LOADINGS OF THE ORIGINAL VARIABLES ON THE FIRST PRINCIPAL COMPONENT IN THE APO-DOSE RESPONSE EXPERIMENT

Variable	First principal Component Loadings
Activity	0.383
Forward locomotion	0.362
Total locomotion	0.366
Hole count	0.360
Hole time	0.310
Corner count	0.274
Corner time	−0.247
Rearing count	0.329
Rearing time	0.298
Habituation	0.166
% variance	64
cross-validation ratio	0.688

Controls n = 13; 0.005 n= 5; 0.01 n = 7; 0.05 n = 11; 0.1 n = 7. The loading vector is scaled to unit length.

photobeam A (or B) gives a count if it is preceded by an interruption of an ACTIVITY photobeam C (or D). A FORWARD LOCOMOTION will also give a TOTAL LOCOMOTION. This corresponds to the rat walking the length of one arm (see arrows in Fig. 1). HOLE COUNT—Interruption of any of the hole photobeams (there is one under each of the six rows of holes) situated 0.5 cm under the hole gives a count. This is nearly always caused by a head dip into the hole. HOLE TIME—The accumulated time that any of the HOLE photobeams is interrupted. CORNER COUNT—Interruption of any of the four vertically oriented photobeams in the corners gives a count. This is a measure of corner restricted behaviour. CORNER TIME—The accumulated time that any of the CORNER photobeams is interrupted. REARING COUNT—Interruption of the horizontally oriented field of photobeams 12.5 cm above the floor gives a count. A count is obtained when a rat raises on its hindlegs. REARING TIME—The accumulated time that a REARING photobeam is interrupted. HABITUATION—was defined as the ratio between the second and the first five-minute periods of ACTIVITY. It is a measure of the within session habituation, low values correspond to a fast rate of habituation.

Experiments and Drugs

Behaviour was recorded in the holeboard apparatus for 10 min. All experiments were run between 9–12 a.m. The order of testing was randomised with respect to treatment. The animals were injected with saline or APO 0.05 mg/kg 15 min prior to testing. Neuroleptics or saline was injected 45 min before testing. Doses were cis-flupenthixol (0.01–0.5 mg/kg), haloperidol (0.01–0.1 mg/kg), metoclopramide (0.2–5 mg/kg), SCH 23390 (0.005–0.05 mg/kg) and sulpiride (0.5–50 mg/kg, 0.5 only in the interaction experiment). The number of animals at each dose level was 4–13, usually 9 in control groups and 6 in the others. All drugs were given SC into the flank in a volume of 1 ml/kg. APO was dissolved in 0.9% saline by rapid heating, cis-flupenthixol (Lundbeck) and SCH 23390 (from Dr. A. Barnett Scheering Plough Co.) were dissolved in 0.9% saline and sulpiride (Delagrange) was dissolved in a minimum quantity of acetic acid and made up to volume by 5% glucose. Commercially available injection solutions of haloperidol (Haldol) and metoclopramide (Primperan) were used and diluted by 0.9% saline.

Statistics

The statistical method employed to analyse the data is called principal component analysis (PCA, see Fig. 2). This method was chosen for two reasons. Firstly the multivariate nature of the holeboard implies that a multivariate statistical method should be employed and we have previously described how PCA can be used on pharmacological data yielding readily interpretable results [29,30]. Secondly, conventional motor activity measurements have been shown to be unreliable and non-selective in that qualitatively different behavioural patterns cannot be discriminated [17]. With PCA the information obtained from the holeboard can be analysed so that qualitatively different patterns of behaviour can be distinguished. The interaction between haloperidol and APO in the present study provides one example.

By PCA the statistical analysis of the interaction between a neuroleptic and APO can be restricted to APO-induced effects. The measure of behaviour is an "APO-score" on a principal component where high values indicate a behaviour similar to that of normal rats and low values indicate behaviour similar to APO treated subjects. Conventional one-way ANOVA and Dunnett's test has been employed to analyse APO-scores. Below follows a more detailed description of PCA illustrated in Fig. 2.

PCA reduces the data to a few orthogonal and uncorrelated dimensions (principal components), each being a linear combination of the originally measured variables [22, 30, 40]. A principal component (PC) may be thought of as a line fitted by least squares to the data scatter in measurement space. The score of each individual rat on a PC is the projection of the data point onto the PC. In order to compensate for scale differences between the measured variables, data were normalised to zero mean and unit variance. The direction of the PC in the measurement space is defined by the loadings. The loadings of the measured variables on the PC is the projection of the point 1.0 on the PC (i.e., the score 1.0) onto each variable. The loading is a measure of the relative importance of a variable for a PC. The dose response curve of APO [29] was subjected to a PCA. The loadings of the measured variables on the first principal component (PC1) of the APO dose-response are given in Table 1. By using the loadings from this previously obtained PC1 (from now on called APO-PC) principal component scores (APO-PC-scores) for new subjects can be calculated. In this way the statistical analysis is restricted to changes along the previously found dose-response axis thus avoiding repeated univariate analysis of correlated variables. Since the behaviour of saline- and APO-controls varied between experiments (as can be seen in Fig. 3a–e) the data on each neuroleptic was separately normalised. The interaction between APO and the neuroleptics was also analysed by separate principal component analyses in order to check for non selective antagonism or the appearance of qualitative shifts in behavioural profile which may show up as second PC's [29,30]. The number of significant components was determined by cross-validation [41]. A cross-validation standard deviation ratio (CVD/SD) below a critical q-value is significant.

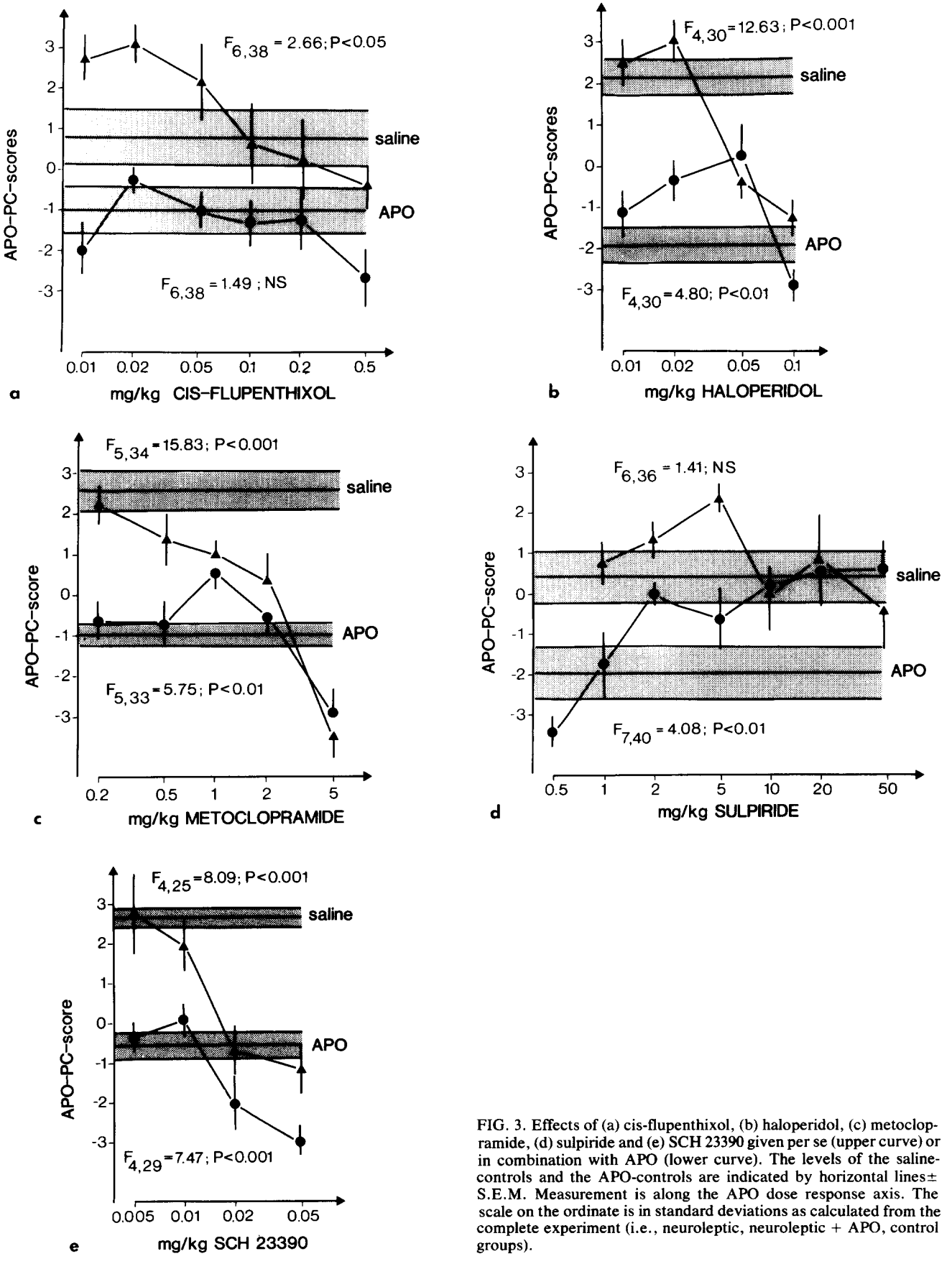

FIG. 3. Effects of (a) cis-flupenthixol, (b) haloperidol, (c) metoclopramide, (d) sulpiride and (e) SCH 23390 given per se (upper curve) or in combination with APO (lower curve). The levels of the saline-controls and the APO-controls are indicated by horizontal lines± S.E.M. Measurement is along the APO dose response axis. The scale on the ordinate is in standard deviations as calculated from the complete experiment (i.e., neuroleptic, neuroleptic + APO, control groups).

TABLE 2

COMPARISON BETWEEN THE APO DOSE-RESPONSE FIRST PRINCIPAL COMPONENT AND THE FIRST PRINCIPAL COMPONENT IN EACH OF THE FIVE DOPAMINE ANTAGONIST EXPERIMENTS

Variable	APO	Cis-Flupenthixol	Haloperidol	Metoclopramide	Sulpiride	SCH 23390
Activity	0.383	0.382	0.408	0.414	0.401	0.408
Forward locomotion	0.362	0.383	0.382	0.410	0.410	0.406
Total locomotion	0.366	0.387	0.394	0.401	0.401	0.329
Hole count	0.360	0.374	0.361	0.362	0.390	0.391
Hole time	0.310	0.349	0.229	0.190	0.329	0.257
Corner count	0.274	0.135	0.293	0.176	−0.008	0.006
Corner time	−0.247	−0.229	−0.149	−0.121	−0.314	−0.150
Rearing count	0.329	0.299	0.338	0.314	0.181	0.352
Rearing time	0.298	0.277	0.299	0.270	0.166	0.348
Habituation	0.166	0.244	0.195	0.341	0.300	0.148
% variance	64.0	56.4	54.8	50.4	49.8	53.5
Cross-val. ratio	0.688	0.728	0.723	0.777	0.760	0.728
Angle with APO	0°	10.0°	8.2°	15.9°	20.9°	17.6°

The loading vectors are scaled to unit length.

RESULTS

Effects of Cis-Flupenthixol

There was a significant dose-related effect of cis-flupenthixol, $F(6,38)=2.66$; $p<0.05$, along the APO-effect axis. Although no single dose produced significantly lower APO-scores than controls, there is a trend to an inhibition of exploration in higher doses (Fig. 3a).

Interaction Between APO and Cis-Flupenthixol

Cis-flupenthixol did not significantly antagonise the inhibition of exploration induced by APO, $F(6,38)=1.49$; NS. The highest doses of cis-flupenthixol had an inhibitory effect on its own adding to the effect of APO (Fig. 3a) as shown by a reduction of the APO-scores compared to rats treated with only APO.

Effects of Haloperidol

There was a significant dose-dependent effect of haloperidol along the APO-PC, $F(4,30)=12.63$; $p<0.001$. In lower doses (0.01 and 0.02 mg/kg) haloperidol had no effect on its own. 0.05 and 0.1 mg/kg inhibited exploration (Fig. 3b) resulting in low APO-scores compared to saline-treated controls.

Interaction Between APO and Haloperidol

There was a significant effect of haloperidol in combination with APO on behaviour (Fig. 3b) along the APO dose-response axis, $F(4,30)=4.80$; $p<0.001$. Haloperidol 0.05 mg/kg significantly antagonised the effect of APO 0.05 mg/kg. At 0.1 mg/kg haloperidol any effect on the APO-induced suppression of exploration was obscured by the inhibitory effect of haloperidol per se.

Effects of Metoclopramide

There was a dose-dependent effect on behaviour (Fig. 3c) as measured on the APO-PC, $F(5,34)=15.83$; $p<0.001$. At 2 and 5 mg/kg metoclopramide significantly inhibited the exploration compared to saline-controls resulting in low APO-scores.

Interaction Between APO and Metoclopramide

Metoclopramide significantly altered the effects of APO, $F(5,33)=5.75$; $p<0.001$. The lowest doses of metoclopramide (0.2 and 0.5 mg/kg) had no effect on the APO induced inhibition of behaviour (Fig. 3c). One mg/kg partially blocked the APO effect while 5 mg/kg had an inhibiting effect on its own.

Effects of Sulpiride

There was no significant effect of sulpiride (Fig. 3d) on exploration as measured on the APO-PC, $F(6,36)=1.41$; NS.

Interaction Between APO and Sulpiride

Sulpiride dose-dependently antagonised the inhibitory effect of APO on exploratory behaviour, $F(7,40)=4.08$; $p<0.01$. The scores on the APO-PC were significantly higher than APO-controls in the groups given 20 and 50 mg/kg (Fig. 3d), doses that did not by themselves affect behaviour (see above). There was a strong tendency to an antagonism of APO at 10 mg/kg ($0.1<p<0.05$).

Effects of SCH 23390

There was a significant effect of SCH 23390 along the APO-PC, $F(4,25)=8.09$; $p<0.001$. Doses of 0.02 and 0.05 mg/kg SCH 23390 significantly inhibited exploration compared to controls (Fig. 3e) resulting in low APO-scores.

Interaction Between APO and SCH 23390

No antagonism of the APO effect could be detected. However, there was a significant effect of SCH 23390 when combined with APO, $F(4,29)=7.47$; $p<0.001$, due to an additive effect of the two compounds (Fig. 3e) resulting in sig-

TABLE 3

LOADINGS OF THE SECOND PRINCIPAL COMPONENT FOUND IN THE HALOPERIDOL APO INTERACTION EXPERIMENT

Variable	Second Principal Component
Activity	0.030
Forward locomotion	0.008
Total locomotion	0.064
Hole count	−0.253
Hole time	−0.535
Corner count	0.347
Corner time	0.476
Rearing count	0.299
Rearing time	0.337
Habituation	−0.308
% variance	19.1
Cross validation ratio	0.957

The loading vector is scaled to unit length.

nificantly lowered APO-scores compared to APO-treated controls.

Principal Component Analyses

The first principal components of each of the five dopamine antagonist experiments were similar to the first principal component of the APO dose-response experiment (Table 2). The angles between APO and sulpiride, SCH 23390 and metoclopramide are 15° or above indicating some difference from the controls. However the objects showing antagonism of the APO-effect did not significantly deviate from the APO-PC as measured by F-tests on the residuals. Only in one instance, the haloperidol experiment, was a second principal component found which was close to significance (cross-validation ratio=0.957, critical value=0.942). This component appeared to be due to effects on the group treated with haloperidol 0.02 mg/kg + APO 0.05 mg/kg. On this component, loadings are particularly high on hole time, rearing and habituation (Table 3).

DISCUSSION

Previous reports on the antagonism by neuroleptics of various low-dose effects of APO have been conflicting. In the present study we found that dopamine antagonists vary considerably in their ability to antagonise the inhibition of exploration induced by a low dose of APO.

Most studies have found that sulpiride antagonises various effects of low doses of APO [3, 7, 15, 21, 28, 37]. However, Ögren *et al.* [24] found that sulpiride is more efficient in young animals while Ålander *et al.* [2] found no effect at all. In man sulpiride antagonises effects of subemetic doses of APO [6]. Interestingly sulpiride has antagonistic properties on APO-induced reduction of dopamine release [37]. In the present study we find that sulpiride in doses between 10 and 50 mg/kg completely and selectively antagonised the effects of APO (Fig. 3d). The antagonism of APO occurred in doses where sulpiride per se did not affect behaviour. Our conclusion is that sulpiride over a relatively wide dose range is a selective dopamine antagonist on receptors mediating inhibition of exploration induced by APO.

Metoclopramide [2], and haloperidol [34] have been reported to block autoreceptors. One group has found that antagonistic effects can be detected but only in a narrow dose range [3]. Kendler *et al.* [15] found no antagonism by these drugs on APO induced inhibition of climbing behaviour.

In the present study we found metoclopramide and haloperidol to be antagonists in a narrow dose-range (Fig. 3b and 3c). In the case of haloperidol there was a deviation into another pattern of behaviour at a dose of 0.02 mg/kg plus APO. This was detected by a separate principal component analysis of the haloperidol APO interaction experiment where a second component reached borderline significance (Table 3). It should be noted that this interaction would have remained undetected or erroneously been interpreted as an antagonistic effect on the APO induced response if conventional statistics had been employed. Our conclusion is that metoclopramide and haloperidol, in a narrow dose-range, can antagonise behavioural effects of APO mediated by the dopamine autoreceptor. Thus, haloperidol and metoclopramide cannot be considered as selective autoreceptor antagonists.

Cis-flupenthixol and SCH 23390 did not antagonise the effect on the APO-induced suppression of exploration. Interestingly these two compounds differ from the others in that their motor inhibitory action adds to the effect of APO (Fig. 3a and 3e).

The dopaminergic nature of the inhibition of exploration induced by the neuroleptics per se has to our knowledge not been substantiated in the literature and it is well known that many neuroleptics affect other neuronal systems than the dopamine systems. Haloperidol and cis-flupenthixol are well known inhibitors of alpha$_1$-adrenergic receptors [14,23] and inhibition of noradrenergic neurotransmission by autoreceptor stimulation is well known to cause a decrease in spontaneous motor activity [33]. However, SCH 23390 has been shown to be a very weak noradrenergic antagonist and SCH 23390 and cis-flupenthixol are both potent 5HT-antagonists [11, 16, 23] while haloperidol and metoclopramide are relatively weak inhibitors [16,23]. Cis-flupenthixol is the only substance exerting antihistamine effects [23] and anticholinergic effects can not account for the inhibition of exploration since the muscarine receptor antagonist scopolamine has been demonstrated to increase, rather than decrease, behavioural activity in the holeboard [30]. Thus, there is little evidence that the inhibition of exploration induced by the neuroleptics tested in the present study exerted their effects via a non-dopaminergic mechanism. It may be added that APO is a selective dopamine agonist with little affinity to other neurotransmitter receptors (see e.g., [16]).

Assuming that the inhibition of exploratory behaviour caused by APO or the neuroleptics (except sulpiride) was due to a reduction of dopamine transmission, the present findings may be interpreted as follows: APO in a low dose selectively stimulates dopamine autoreceptors, resulting in a decrease in the release of dopamine in the synaptic cleft. Cis-flupenthixol and SCH 23390 selectively block postsynaptic dopamine receptors (see also [9,10]) i.e, not autoreceptors. Therefore the combined treatment with e.g., SCH 23390 and APO, result in an additive inhibition of dopamine transmission and, consequently, exploratory behaviour. This is seen as a parallellity between the dose-response curves for SCH 23390 alone and SCH 23390 plus APO (Fig. 3e) and similarly for cis-flupenthixol (Fig. 3a). In

contrast to the above haloperidol and metoclopramide antagonise both autoreceptors *and* postsynaptic receptors. The ability of e.g., metoclopramide, to antagonise the APO-effect on exploration is thus due to an inhibition of autoreceptors. At the same doses metoclopramide per se begins to inhibit exploration by antagonism of postsynaptic receptors. The inhibition of exploration seen following higher doses of metoclopramide in combination with APO is therefore solely due to the postsynaptic blockade by metoclopramide. Thus, the dose-response curves for metoclopramide and metoclopramide plus APO join at a point where both the postsynaptic and the autoreceptor antagonistic properties are evident.

Although the above model can explain the data from the present study it is in conflict with findings from other studies. Starke *et al.* [32] studying ^{3}H-acetylcholine release from the rabbit caudate nucleus and Herrera-Marschitz and Ungerstedt [9] studying rotational behaviour in rats with kainic acid or 6-OHDA lesions in the caudate nucleus have amply demonstrated that sulpiride has postsynaptic dopamine receptor blocking properties. It has also been shown that sulpiride antagonises APO-induced locomotor behaviour [20] which is considered to be a postsynaptic effect. To fit these data together, the existence of at least two pharmacologically distinct classes of postsynaptic dopamine receptors must be postulated: one selectively antagonised by sulpiride and one *not* sensitive to sulpiride but sensitive to the other neuroleptics used in this study. The autoreceptors and the postsynaptic sulpiride-sensitive receptors may be pharmacologically identical. It should be noted that the inhibition of exploration induced by APO may be mediated by a population of postsynaptic receptors, however this does not change the pharmacological conclusion concerning dopamine receptor subclassification.

The discrepancies between the results of the present study and some other studies may partly be explained by quite large differences in experimental design [17,24]. The present study has employed a multivariate recording method [19] and data has been subjected to a detailed statistical analysis [22, 29, 30, 40] aimed at describing major sources of variation. In this way we have tried to ensure that an antagonist is specific (i.e., to test if the interaction between an agonist and an antagonist result in qualitative changes in behaviour) as far as the recording device is able to record different aspects of the animals' behaviour. For example, while the rats treated with sulpiride 20 mg/kg plus APO were indistinguishable from saline treated controls haloperidol 0.02 mg/kg (Table 3) antagonised only some aspects of the APO effects on exploration, i.e., not all variables were normalised. Thus sulpiride but not haloperidol is in our hands a specific antagonist of APO. In case a recording device is used which only detects such aspects of behaviour found to be affected by haloperidol 0.02 mg/kg, this drug appears to be a specific antagonist. This finding may explain why haloperidol has been found to be an autoreceptor antagonist by some investigators [3, 7, 34] but not others [15,24].

In conclusion, out of the five dopamine antagonists investigated only sulpiride selectively blocks low-dose effects of APO. Thus, sulpiride can be employed to test if a putative dopamine receptor agonist has the same properties as a low dose of APO. It is suggested that inhibition of exploration caused by APO is mediated by one class of pharmacologically distinct dopamine receptors while the inhibition of exploration caused by, e.g., SCH 23390 and cis-flupenthixol, may be mediated by another class of dopamine receptors. Haloperidol and metoclopramide were non-selective antagonists.

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