mediated indirectly via the release of cyclo-oxygenase products unlike some other SRS-A induced responses (Piper et al 1981).

Responses of both preparations to SRS-A were blocked by FPL 55712, however, our results demonstrate two differences in the effects of FPL 55712 on these preparations. Firstly, FPL 55712 is a less potent antagonist on the fundus than on the ileum and secondly, whereas a contact time of 10 min was sufficient to achieve equilibrium on the ileum, 60 min was necessary on the fundus. One possible explanation for the potency difference is that the receptors in the ileum are different from those in the fundus. However, there are many factors unrelated to receptor differences which can influence the potency of antagonists, for example the presence of inactivation processes for the agonist (Furchgott 1972), and further quantitative studies with synthetic leukotrienes will be necessary to resolve this question.

The finding that FPL 55712 equilibrates more rapidly on the ileum than on the fundus has implications for the use of this compound as a pharmacological tool. FPL 55712 has been shown to be a potent antagonist of the actions of SRS-A on guinea-pig ileum using contact times as short as 15 s (Augstein et al 1973). Our data show that not only does the potency of FPL 55712 vary between tissues but the equilibration time also varies. Therefore when this compound is used as a tool to investigate the involvement of leukotrienes in anaphylactic reactions (Chand 1979) it will be necessary to establish both the potency and contact time for the tissue under study before valid conclusions can be drawn.

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Communicated March 15, 1982

0022–3573/82/090588–03 $02.50/0


# Behavioural actions of neuroleptics are not reduced by hypophysectomy

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The behavioural effects and biochemical changes in cerebral dopamine systems caused by sulpiride treatment testify to benzamide action on the central nervous system. Yet, notwithstanding these indices of changed brain activity, sulpiride has a very low penetration into brain tissue (Benakis & Rey 1976) and it has been considered that sulpiride may influence structures outside the blood-brain barrier, such as the pituitary, to indirectly modify central events (Portaleone et al 1978). Thus, we have studied the effects of hypophysectomy on both the behavioural effects and brain penetration of neuroleptic drugs.

*Method*

Normal, sham-operated and hypophysectomized male Sprague-Dawley (CD) rats were obtained from Charles River UK Ltd and were maintained under identical conditions except that the hypophysectomized rats received a supplement of sodium chloride in their drinking water. The success of hypophysectomy was indicated by the maintenance of a constant body weight by the lesioned rats (127·7 ± 2·6 g; the weights of sham-operated animals being 329·6 ± 4·3 g), and absence of pituitary tissue on histological examination at completion of the studies. For behavioural testing, carried out between 08.00 and 18.00 h, animals were taken from normal housing of 6 per cage and allowed 30 min to adapt to individual observation/testing cages. The presence of catalepsy was detected by placing animals' front limbs over a horizontal bar; the intensity of catalepsy was determined as the time an animal

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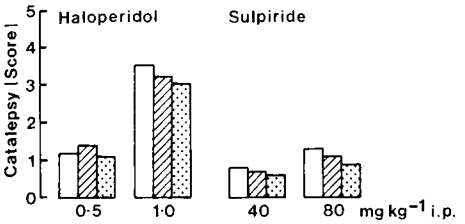


FIG. 1. Catalepsy induced by haloperidol, 0·5 and 1·0 mg kg$^{-1}$ i.p., and sulpiride, 40 and 80 mg kg$^{-1}$ i.p., in normal (open columns), sham-operated (hatched columns) and hypophysectomized rats (stippled columns). Catalepsy was scored on the 0–5 system described in the text. n = 6–10. S.e.m.s <14%. There were no significant differences ($P > 0.05$, Student's $t$-test) in responses of the three groups of rats to either neuroleptic.

remained in this abnormal position and, to account for infinite periods of time, the following scoring system was used to designate intensity, 0·1–2·5 min = 1, 2·6–5·0 min = 2, 5·1–10·0 min = 3, 10·1–20·0 min = 4, 20·1 min – ∞ = 5 (see Costall & Naylor 1974). Stereotypy was scored according to the system 1 = discontinuous sniffing, repetitive head and limb movements, 2 = continuous sniffing, repetitive head and limb movements, 3 = discontinuous biting, gnawing or licking, 4 = continuous biting, gnawing or licking. In the drug distribution studies [$^3$H]haloperidol (21·4 Ci mmol$^{-1}$, Amersham), [$^3$H]sulpiride (26·2 Ci mmol$^{-1}$, Amersham) and [$^{14}$C]nomifensine (0·5 Ci mmol$^{-1}$, Hoechst) were administered with non-labelled material to give 50 μCi kg$^{-1}$ i.p. in doses of 1·0, 40·0 and 5·0 mg kg$^{-1}$ respectively. After suitable times (see below) rats were killed by cervical dislocation and blood samples taken. Brains were perfused via the aorta with 40 ml ice cold 0·9% NaCl (saline) and the brain areas dissected out over ice. The pineal gland, pituitary gland, cerebellum, pons and medulla, and hippocampus were taken in their totality, an approximate 50 mg sample of frontal cortex was taken, and remaining areas dissected from serial sections (approximate weights indicated): caudate-putamen (40 mg), globus pallidus (10 mg), nucleus accumbens (10 mg), tuberculum olfactorium (10 mg), hypothalamus (10 mg) and thalamus (20 mg). Tissues were placed in cones, weighed and then burnt in a tissue oxidizer with collection of $^3H_2O$ or $^{14}CO_2$; oxidizer efficiency $^3$H—98%, $^{14}$C—99%. Samples were subsequently counted in a Packard Tricarb liquid scintillation spectrometer; spectrometer efficiency $^3$H—45%, $^{14}$C—67%.

Table 1. Distribution of [$^{14}$C]nomifensine, [$^3$H]sulpiride and [$^3$H]haloperidol in the brains of sham-operated (Sham) and hypophysectomized (Hypo.) rats.

| | [$^{14}$C]Nomifensine | | [$^3$H]Sulpiride | | [$^3$H]Haloperidol | |
|---|---|---|---|---|---|---|
| Tissue | Sham. | Hypo. | Sham | Hypo. | Sham | Hypo. |
| Blood | 1·0 | 1·0 | 1·0 | 1·0 | 1·0 | 1·0 |
| Pineal gland | 9·4 | 10·1 | 2·3 | 2·3 | 11·3 | 10·9 |
| Pituitary | 6·8 | — | 1·9 | — | 5·5 | — |
| Cerebellum | 3·1 | 2·1 | 0·07 | 0·06 | 2·2 | 2·5 |
| Pons & medulla | 3·1 | 2·5 | 0·05 | 0·05 | 1·8 | 2·5 |
| Frontal cortex | 4·2 | 2·6 | 0·08 | 0·09 | 2·5 | 3·7 |
| Tuberculum ol. | 4·3 | 3·6 | 0·15 | 0·12 | 2·9 | 3·5 |
| Nucleus accumbens | 5·5 | 4·2 | 0·11 | 0·13 | 3·8 | 3·5 |
| Hypothalamus | 3·5 | 2·7 | 0·10 | 0·11 | 2·1 | 2·9 |
| Thalamus | 4·3 | 3·3 | 0·05 | 0·08 | 2·5 | 2·4 |
| Globus pallidus | 5·6 | 3·2 | 0·09 | 0·06 | 3·6 | 2·6 |
| Caudate putamen | 4·8 | 3·2 | 0·04 | 0·06 | 3·7 | 2·4 |
| Hippocampus | 4·2 | 3·0 | 0·08 | 0·11 | 2·1 | 2·5 |

Each value is the mean of 6 determinations, the values being initially determined as d min$^{-1}$ mg$^{-1}$ tissue/blood and then expressed relative to the blood concentration indicated as 1. Standard errors, calculated on the original data, were in a range of 4–19%. A comparison of data (Student's $t$-test) indicated no significant difference between values obtained for sham-operated or hypophysectomized rats.

*Results*

Preliminary experiments showed haloperidol to induce dose-related catalepsy in normal rats at 0·5–4·0 mg kg$^{-1}$ i.p. (Janssen, prepared in 1% lactic acid), although sulpiride (SESIF, prepared in minimum quantity HCl) caused only a weak catalepsy (score 1) which was not dose-dependent (40–160 mg kg$^{-1}$ i.p.). Submaximal doses of haloperidol, 0·5 and 1·0 mg kg$^{-1}$ i.p., and sulpiride used at 40 and 80 mg kg$^{-1}$ i.p., caused indistinguishable cataleptic responses in normal, sham-operated and hypophysectomized rats (Fig. 1). (+)-Amphetamine (Aldrich, prepared in minimum quantity of HCl, 1·5–10·0 mg kg$^{-1}$ i.p.) and nomifensine (hydrogenmaleinate, Hoechst, prepared in minimum quantity of HCl, 5·0–30·0 mg kg$^{-1}$ i.p.) caused dose-related stereotyped behaviour which was markedly enhanced by hypophysectomy (sham-operated and normal rats gave the same response); the enhancement was most clearly seen at lower doses where reduced onset, increased intensity and prolonged duration of

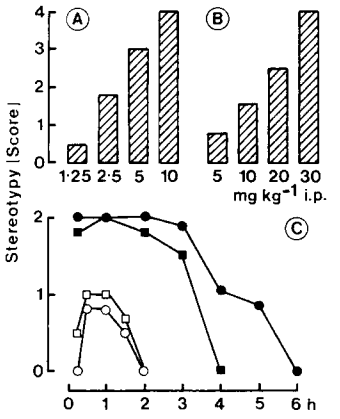


FIG. 2. Dose-dependency of stereotyped behaviour induced in normal rats by A. (+)-amphetamine and B. nomifensine. C indicates stereotypy induced by 1·5 mg kg$^{-1}$ (+)-amphetamine in sham-operated (□) and hypophysectomized (■) rats, or by 5·0 mg kg$^{-1}$ i.p. nomifensine in sham-operated (○) and hypophysectomized rats (●). Stereotypy was scored on the 0–4 system described in the text. n = 6–10. S.e.m..s <10%. The enhancement of intensity (scored), shorter onset and prolonged duration of stereotypic effects in the hypophysectomized animals were significant to $P < 0.001$ (Student's $t$-test).

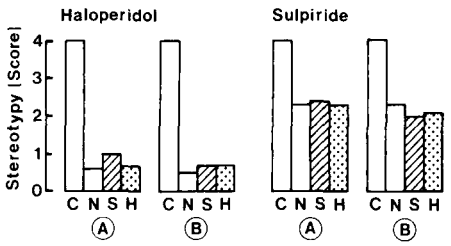


FIG. 3. Antagonism by haloperidol, 0·05 mg kg$^{-1}$ i.p., and sulpiride, 160 mg kg$^{-1}$ i.p., of stereotypy induced by A. 10·0 mg kg$^{-1}$ i.p. (+)-amphetamine and B. 30 mg kg$^{-1}$ i.p. nomifensine in normal (N, open columns), sham-operated (S, hatched columns) and hypophysectomized rats (H, stippled columns). C indicates control responses to the stereotypic agents in the presence of solvent for the neuroleptics. Stereotypy was scored on the 0–4 system described in the text. n = 6–10. S.e.m.s <7%. Antagonism of stereotypy by haloperidol and sulpiride in N, S and H significant to $P < 0{\cdot}001$ in all experiments. There was no significant difference between N, S and H in any situation.

stereotypic action were apparent (Fig. 2). Haloperidol at 0·05 mg kg$^{-1}$ i.p., the minimum dose shown to reliably reduce stereotypic behaviour, and sulpiride at 160 mg kg$^{-1}$ i.p., causing a modest reduction in stereotypy, were equieffective in the normal, sham-operated and hypophysectomized animals, both against (+)-amphetamine (10 mg kg$^{-1}$ i.p.) and nomifensine (30 mg kg$^{-1}$ i.p.) (Fig. 3).

[$^3$H]Haloperidol accumulated in brain tissue, most markedly in structures outside the blood-brain barrier (pituitary gland and pineal gland). Whilst [$^3$H]sulpiride also accumulated in the pituitary and pineal glands, levels in the remainder of the brain were conspicuously low. However, for both [$^3$H]sulpiride and [$^3$H]haloperidol brain levels were the same in both the sham-operated and hypophysectomized rats. Similarly for [$^3$H]nomifensine, whilst there was a consistent trend for a lower accumulation in the brains of hypophysectomized animals, the modest reductions, approximately 25%, were never significnt.

*Discussion*

To show an essential involvement of pituitary function with neuroleptic effects would have profound implications for the understanding of neuroleptic action. This was clearly suggested by the ability of hypophysectomy to prevent sulpiride-induced increase in brain DOPAC levels (Portaleone et al 1978) and to prevent striatal dopamine receptor supersensitivity to chronic haloperidol treatment (Hruska et al 1980). However, with respect to a behavioural assessment, the present study showed that hypophysectomy did not modify the cataleptic activity or reduce the antistereotypic activities of haloperidol and sulpiride. (The effect of hypophysectomy to enhance amphetamine stereotypy itself makes it difficult to comment as to whether haloperidol was more effective in antagonizing stereotypy after hypophysectomy.) It is therefore interesting that the more recent studies by Jenner et al (1981a,b) have shown that hypophysectomy does not prevent the increased cerebral dopamine turnover following sulpiride administration, or the development of striatal dopamine receptor supersensitivity induced by repeated haloperidol treatment. Additionally the present study shows that hypophysectomy does not modify the penetration of [$^3$H]haloperidol or [$^3$H]sulpiride into the brain. The present study and the findings of Jenner et al (1981a,b) argue against a significant pituitary involvement with neuroleptic action on cerebral dopamine systems. However, an obvious increase in amphetamine stereotypy and hyperactivity was recorded after hypophysectomy in the present study, and Benakis (1978) and Perry et al (1981) have reported that hypophysectomy can induce behavioural hypersensitivity to amphetamine (hyperactivity) and apomorphine (stereotypy). It was considered that the increased stereotypy observed with amphetamine and nomifensine in hypophysectomized rats may indicate a greater drug penetration into brain tissue. However, the administration of [$^{14}$C]nomifensine, in reasonable pharmacological dosage, showed a similar pattern of distribution in both sham-operated and hypophysectomized animals. Whilst accepting that these observations do not permit any comment as to drug binding to specific and non-specific binding sites, a cautious conclusion is a lack of effect of hypophysectomy on the total binding of [$^{14}$C]nomifensine to rat brain tissue. Further studies using in vivo receptor labelling methodology would be required to detect any change in receptor binding. In any event, it is hypothesized that the pituitary may retain an ability to modify cerebral dopamine function irrespective of a non-involvement with neuroleptic action.

This work was supported by the Medical Research Council. Gifts of drugs were received from Hoechst and SESIF, France.

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