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The effect of chronic haloperidol treatment on some cardiovascular parameters in cats

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1 Blood pressure, heart rate and evoked cardiovascular reflexes were examined in cats following chronic treatment with haloperidol, at a dose of 1 mg kg^{-1} per day, orally for 23 days. Five days after the final dose the animals were anaesthetized and tested for their reaction to various cardiovascular stimuli and to a number of agonist and antagonist drugs, given both intravenously and into the vertebral artery.

2 It was found that treatment with haloperidol caused hypertension in the cats, as well as a potentiation of the pressor response to bilateral carotid occlusion. The response to 30° head-up tilting was also altered so that in treated cats, the blood pressure returned to normal more rapidly during the tilt.

3 There was no difference in the heart rate of the two groups of cats, nor in the pressor response to intravenous noradrenaline or angiotensin II or to afferent brachial nerve stimulation, nor was the depressor action of bradykinin altered. Hexamethonium reduced the blood pressure in both control and treated cats to approximately the same level. Blood O_2, CO_2, pH and bicarbonate levels were also unaltered by the treatment, as was plasma renin activity.

4 Of the drugs given into the vertebral artery, only noradrenaline, prazosin, ketanserin and haloperidol caused a significantly greater fall in blood pressure in treated than in control cats, while clonidine and St91 were equally effective in both groups. These results suggest that haloperidol treatment has caused a greater modulation of central α_1- than of α_2-adrenoceptors.

Introduction

It has been shown that the chronic treatment of animals with haloperidol or other major tranquillizers can cause a sensitization of central catecholamine receptors. Dunstan & Jackson (1976) reported that mice treated chronically with haloperidol became considerably more sensitive to the stimulant effects of both clonidine and dexamphetamine. This supersensitivity was abolished by treatment with α-adrenoceptor antagonists. Møller-Neilsen *et al.* (1978) and Muller & Seeman (1977) have also shown an increased sensitivity to dopamine agonists following chronic treatment with neuroleptic drugs, while Head *et al.* (1979) have shown that chronic haloperidol treatment can also enhance the analgesic potency of morphine.

It therefore seemed of interest to study the effects of withdrawal from chronic haloperidol treatment on cardiovascular responsiveness, since central catecholamine mechanisms have been implicated in central control of the cardiovascular system (Chalmers, 1975). Accordingly the resting mean systemic blood pressure and heart rate of cats so treated was measured, as well as the response of these animals to various manoeuvres which cause reflex cardiovascular changes, and to drugs given both intravenously (i.v.) and into the vertebral artery (i.v.a.).

Methods

Cats of either sex, weighing 2–5 kg, were dosed with 1 mg kg^{-1} haloperidol daily, given in their food for 23 days. Control cats were held under identical conditions, but received no haloperidol. Five days after the last dose of the drug, the cats were anaesthetized with chloralose (80 mg kg^{-1} i.v.) after induction with halothane and nitrous oxide, and were set up for recording blood pressure and heart rate. The right brachial nerve bundle was exposed and electrodes were placed in position for stimulating at a frequency of 100 Hz for 10 s with a pulse duration of 0.7 ms using 12 volts (Johansson 1962). Reflex responses to 30°

head-up tilting for 120 s and to bilateral carotid occlusion (B.C.O.) for periods of 30 s were also studied.

The animals were set up on a Mytton surgical table to allow tilting. Intravenous noradrenaline (0.03 and 0.06 $\mu g\,kg^{-1}$) was used to test for peripheral α-adrenoceptor sensitization. To ensure a stable anaesthetic state during the experiment a constant infusion of chloralose (1 $mg\,ml^{-1}$) was given at a rate of 0.1 $ml\,min^{-1}$ throughout the experiment and a body temperature of 36°–37°C was maintained. For intravertebral artery infusions, the cats were placed on artificial respiration and the chest was opened. The left subclavian artery and its side branches were exposed. All these branches except the vertebral artery were ligated and a cannula was inserted into the subclavian artery. This was advanced until its tip lay opposite the origin of the vertebral artery and was then tied in place. The cannula was attached to a Palmer slow infusion pump. Drugs were given into the vertebral artery in a volume of 2.0 ml, infused over a 2 min period and were washed in with a further 2 ml of saline. Where applicable, data presented refer to the changes in mean systemic blood pressure or heart rate (± s.e.mean) and statistical significance was evaluated by means of Student's *t* test.

The drugs used were: amphetamine hydrochloride (Burroughs Wellcome), angiotensin II (Ciba), bradykinin (Sigma), α-chloralose (Merck), clonidine hydrochloride (Calbiochem.), dopamine hydrochloride (Sigma), haloperidol (Searle), hexamethonium tartrate (May & Baker), 5-hydroxytryptamine creatinine sulphate (Sigma), ketanserin tartrate (Janssen), methoxamine base (Burroughs Wellcome), morphine hydrochloride (MacFarlan Smith), (−)-noradrenaline bitartrate (Sigma), (−)-phenylephrine hydrochloride (ICN Pharmaceuticals), piperoxan hydrochloride (May & Baker), prazosin hydrochloride (Pfizer) and St91 (2-(2,6-diethylphenylimino)-2-imidazolidine hydrochloride) (Boehringer/Ingelheim).

Table 1 The effect of withdrawal from chronic haloperidol pretreatment on resting blood pressure and heart rate, some evoked cardiovascular reflexes and the responses to vasoactive drugs

		Control	*Treatment*
Resting values			
Blood pressure (mmHg)		124.7 ± 3.8	155.9* ± 3.2
Heart rate (beats min)		141.9 ± 2.7	148.2 ± 3.6
Evoked reflexes			
Bilateral carotid occlusion		+ 37.4 ± 2.8	+ 53.3* ± 2.3
Brachial nerve stimulation		+ 16.3 ± 1.6	+ 17.3 ± 1.8
30° head-up tilting			
(i) mmHg fall		− 7.3 ± 1.3	− 6.2 ± 0.8
(ii) duration of fall (s)		99.5 ± 7.2	51.8* ± 4.3
Blood pressure responses to intravenous agonist drugs			
(i) Noradrenaline	0.03 $\mu g\,kg^{-1}$	19.9 ± 0.9	19.8 ± 0.8
	0.06 $\mu g\,kg^{-1}$	29.9 ± 1.5	29.1 ± 0.8
(ii) Angiotensin II	0.5 $\mu g\,kg^{-1}$	24.8 ± 1.4	26.1 ± 1.6
	1.0 $\mu g\,kg^{-1}$	45.2 ± 1.3	46.3 ± 2.0
(iii) Bradykinin	5.0 $\mu g\,kg^{-1}$	−21.0 ± 1.2	−22.0 ± 1.2
	10.0 $\mu g\,kg^{-1}$	−41.7 ± 1.7	−42.2 ± 1.5

$n = 65$. Mean values are given ± s.e.mean.
*Significant difference ($P < 0.01$) between control and test groups.

Results

Effects on blood pressure, heart rate, and cardiovascular reflexes

It was found that the cats which had been pretreated chronically with haloperidol were all hypertensive, as compared with the control cats. The mean resting blood pressure of the treated cats was 155.9 ± 3.2 mmHg, while that of the controls was 124.7 ± 3.8 mmHg. However, there were no significant differences in the heart rates of the two groups (Table 1).

Withdrawal from haloperidol also altered the response to BCO so that the magnitude of the pressor response was approximately doubled in the treated cats. The effect of tilting was also changed after haloperidol. While the initial fall in blood pressure was not significantly different between the two groups of cats, the duration of the orthostatic hypotension was almost halved by the treatment. In control cats, the mean time required for the blood pressure to return to the supine level was 99.5 ± 7.2 s, while in the treated cats, full recovery occurred in 51.8 ± 4.3 s (Table 1).

Withdrawal from haloperiol had no effect on the pressor response to brachial nerve stimulation, or to i.v. noradrenaline (Table 1) nor did it affect the changes in the heart rate caused by these stimuli.

Studies on the mechanism of hypertension

Blood parameters The following blood parameters were measured (in both control and haloperidol-treated cats) with a Corning model 168 Blood Gas Analyser ($n = 13$ for each group): pH, P_{O_2}, P_{CO_2}, [HCO_3] and base excess. In no case was there a significant difference between the two groups of cats. Plasma renin activity was also measured by radio-

immunoassay. ($n = 20$ in each group). Again, there was no significant difference between the treated and control groups.

Responses to drugs given intravenously Bradykinin, 5.0 and 10.0 $\mu g\,kg^{-1}$ and angiotensin II 0.5 and 1.0 $\mu g\,kg^{-1}$ were given i.v. There were no significant differences in the pressor response to angiotensin ($n = 7$) or bradykinin ($n = 8$) between the control and test groups (Table 1).

Hexamethonium, 10 $mg\,kg^{-1}$ was given i.v. to five treated and five control cats. This caused a mean fall in blood pressure of 19.7 ± 2.7 mmHg in the control cats, but in the treated cats, the fall was significantly larger (45.4 ± 3.1 mmHg), so that the blood pressure fell to approximately the same level in both groups, and persisted at this level for at least 2 h (Table 3). Dose-response curves to i.v. noradrenaline were constructed in the cats before and after receiving hexamethonium. There was no significant difference in the dose-response curves between control and treated cats either before or after the ganglion blockade.

Effects of drugs infused into the vertebral artery The following drugs were infused into the vertebral artery of control and treated cats: clonidine 1 $\mu g\,kg^{-1}$, St91 10 $\mu g\,kg$, noradrenaline 20 $\mu g\,kg^{-1}$, methoxamine 200 $\mu g\,kg^{-1}$, phenylephrine 40 $\mu g\,kg^{-1}$, amphetamine 200 $\mu g\,kg^{-1}$, dopamine 20 and 80 $\mu g\,kg^{-1}$, 5-hydroxytryptamine 10 $\mu g\,kg^{-1}$, piperoxan 200 $\mu g\,kg$, prazosin 2 $\mu g\,kg^{-1}$, haloperidol 100 $\mu g\,kg^{-1}$, ketanserin 100 $\mu g\,kg^{-1}$ and morphine 1 $mg\,kg^{-1}$. Groups of five animals were used for each drug. Methoxamine and phenylephrine caused a small but not significant pressor effect, lasting 60–90 s after the end of the infusion, while with amphetamine, the small pressor effect lasted for at least 1 h. However, none of these three drugs caused a significantly different response between control and treated cats. This response is probably due to a spill-over of part of the infused drugs into the systemic circulation. Neither dopamine nor 5-hydroxytryptamine had any significant effect on blood pressure in either group of cats. However, clonidine, St91, and noradrenaline all caused a long-lasting hypotensive effect, after an initial small, brief rise in blood pressure. Only with noradrenaline was this hypotension significantly larger in the treated than in the control cats (Table 2).

Piperoxan caused a small but not significant rise in blood pressure in both groups, while prazosin, haloperidol, and ketanserin all produced a long-lasting hypotension. This was significantly greater in the treated cats with the latter three drugs (Table 3), but there was no difference with piperoxan.

Morphine also caused a large fall in blood pressure. While this was larger in the control than in the treated group, the difference was not significant (Table 3).

Most of the drugs used caused a small fall in heart rate (10 to 40 beats min^{-1}), though with piperoxan, amphetamine, dopamine, and 5-hydroxytryptamine, both increases and decreases in heart rate occurred,

Table 2 Changes in blood pressure following infusion of agonist drugs into the vertebral artery of control and haloperidol-treated cats

Drug	*Control* (mmHg)	*Treated* (mmHg)
Noradrenaline 20 $\mu g\,kg^{-1}$	−14.4 ± 2.8	−31.7* ± 3.1
Clonidine 1 $\mu g\,kg^{-1}$	−30.4 ±10.2	−29.0 ±14.8
St91 10 $\mu g\,kg^{-1}$	−15.0 ± 6.7	−25.0 ±11.2
Methoxamine 200 $\mu g\,kg^{-1}$	+ 5.8 ± 2.6	+12.3 ± 9.1
Phenylephrine 40 $\mu g\,kg^{-1}$	+ 6.3 ± 6.2	− 1.3 ± 1.2
Amphetamine 200 $\mu g\,kg^{-1}$	+ 8.8 ± 6.3	+10.5 ± 6.8
Dopamine 80 $\mu g\,kg^{-1}$	− 2.5 ± 1.2	− 1.7 ± 0.8
5-Hydroxytryptamine 10 $\mu g\,kg^{-1}$	− 3.0 ± 1.9	− 5.6 ± 3.8

$n = 5$ all groups. Values are mean ± s.e.mean
Figures marked * are significantly different ($P < 0.05$) from the corresponding control group.

Table 3 Changes in blood pressure following infusion of antagonist drugs or morphine into the vertebral artery of control and haloperidol-treated cats

Drug	*Control* (mmHg)	*Treated* (mmHg)
Piperoxan 200 $\mu g\,kg^{-1}$	+ 6.5 ± 4.2	+ 4.0 ± 2.9
Prazosin 2 $\mu g\,kg^{-1}$	−16.0 ± 4.9	−37.7* ±11.8
Ketanserin 100 $\mu g\,kg^{-1}$	−47.0 ± 4.6	−65.6* ± 2.0
Haloperidol 100 $\mu g\,kg^{-1}$	−10.6 ± 3.9	−37.0* ±11.3
Morphine 1 $mg\,kg^{-1}$	−52.0 ±16.2	−39.4 ±12.8
Hexamethonium 10 $mg\,kg^{-1}$	−19.7 ± 2.7	−45.4* ± 3.1

$n = 5$ for all groups. Values are mean ± s.e.mean.
Figures marked * differ significantly ($P < 0.05$) from the corresponding control group.

while prazosin and noradrenaline produced a slight tachycardia in all cases. However, none of these drugs had any differential effect on the treated and control cats.

Discussion

The dosing regime used in this study, namely 1 mg kg^{-1} per day, orally for 23 days, followed by five days withdrawal was found to produce significant changes in the cardiovascular parameters studied, and was therefore used throughout the study. No attempt was made to determine whether other regimes could in fact produce greater changes, nor were dose-response curves prepared to haloperidol. There are numerous published papers indicating that changes in the sensitivity of various central receptor types can be produced following a variety of dosing regimes, suggesting that this is not a critical factor in producing the changes (see, for example Dunstan & Jackson, 1976; 1977 a and b; 1978; 1979; Bannon *et al.*, 1980; Kamer *et al.*, 1981). There is limited information on the cardiovascular effects of chronic neuroleptic treatment. Lang *et al.* (1966) who used dogs, have studied the effects of both acute and chronic chlorpromazine on resting blood pressure, and on the response to i.v. noradrenaline. They found that single doses of chlorpromazine caused hypotension, and reduced the pressor effects of noradrenaline. In contrast, the basal blood pressure slowly rose after chronic treatment with chlorpromazine, and achieved statistical significance after 60 days treatment. The pressor response to noradrenaline also increased with time, and became significantly greater than the control after 75 days treatment. Perrington *et al.* (1980) have reported that, while rats treated chronically with haloperidol became hyperkinetic several days after withdrawal from the drug, their basal blood pressure was not significantly different from control rats. Similarly, there was no change in their cardiovascular response to either phenylephrine or clonidine.

In the present study, quite different results were obtained. It was found that when cats were withdrawn from haloperidol, they became hypertensive, although there was no significant change in heart rate. In addition, the pressor response to bilateral carotid occlusion was considerably augmented, and, when the cats were subjected to a 30° head-up tilt, the resulting fall in blood pressure was of shorter duration than in control cats. In contrast, the pressor response to brachial nerve stimulation, or to i.v. noradrenaline was not altered, nor were there differences between the control and treated cats in the heart rate changes produced by any of these stimuli. Johansson (1962) has shown that the cardiovascular reflexes resulting from brachial nerve stimulation have different central and efferent pathways from those caused by baroreceptor stimulation, and the present results are consistent with this.

As mentioned in the introduction, haloperidol treatment is known to cause sensitivity changes in several different central receptor types. These include opioid (Head *et al.*, 1979), dopamine (Anden *et al.*, 1970; Møller-Neilsen *et al.*, 1978; Muller & Seeman, 1977), 5-hydroxytryptamine and α-adrenoceptors (Anden *et al.*, 1970; Muller & Seeman, 1977). The present study was designed to provide information to indicate whether any or all of these receptor types were involved in the hypertension. It was clear that the change in the blood pressure was not of peripheral origin, since the responses to i.v. noradrenaline, bradykinin, and angiotensin were not altered by the haloperidol treatment. Similarly, there was no change in the plasma renin activity or the blood chemistry of the treated cats.

After injecting hexamethonium, the blood pressure of both groups of cats fell to approximately the same level, further confirming that the hypertension in the treated group was not of peripheral origin. Of the agonist drugs used that were given into the vertebral artery, only noradrenaline and clonidine caused persistent hypotension and only with noradrenaline was this greater in the treated than the control cats. Morphine also caused a large and persistent fall in blood pressure but again this effect did not differ significantly between the two groups. All the other agonist drugs used caused at the most, brief and small changes in blood pressure, presumably due to spillover from the cerebral to the systemic circulation. The lack of action of these drugs may be due to failure to penetrate to possible sites of action, or to the fact that the vertebral artery does not supply sites of action relevant to cardiovascular control.

In contrast, several of the antagonist drugs caused greater hypotension in treated than in control cats. These were prazosin, ketanserin, and haloperidol. All these three drugs have considerable α-adrenoceptor antagonist activity (Janssen *et al.*, 1968; Anden *et al.*, 1978; van Neuten *et al.*, 1981) although ketanserin and haloperidol also have strong 5-hydroxytryptamine and dopamine antagonist action respectively. Since neither 5-hydroxytryptamine nor dopamine, given i.v.a. had any significant cardiovascular effects, it seems probably that the α-adrenoceptor antagonist action is the relevant property in this instance. Copeland & Bentley (1985) have shown that both prazosin and ketanserin at the doses used in this study can cause hypotension by a central action without any peripheral vascular effects.

Piperoxan, which has greater antagonist potency at α_2- than at α_1-adrenoceptors (Starke, 1981) did not cause hypotension but rather, a small though not significant rise in blood pressure in both groups of cats.

Thus this study does not provide evidence that chronic haloperidol pretreatment has caused any modulation of central 5-hydroxytryptamine, dopamine, opioid, or α_2-adrenoceptors that can affect the blood pressure. However, there are indications that central α_1-adrenoceptors have become more sensitive to antagonist drugs and it is possible that this is the cause of the hypertension and enhanced sympathetic reflexes seen after haloperidol withdrawal. Philippu *et al.* (1971) have shown that noradrenaline given into the posterior hypothalamus causes hypertension, and it may be that this is the site of the present haloperidol-induced hypertension. Philippu & Stroehl (1978) implicated β-adrenoceptors in the hypertension but in the present study, no drugs selective for the β-receptor were used. The fall in blood pressure caused by noradrenaline would presumably be via α_2-adrenoceptors though it is puzzling that it caused a greater fall in treated than in control cats, while clonidine was equally effective in both groups. It is also puzzling that there was no indication of modulation of any central receptors governing heart rate. More exact information on these points will require the direct administration of the relevant drugs to more restricted areas of the brain.

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