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Different effects of chronic administration of haloperidol and pimozide on dopamine metabolism in the rat brain

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Abstract

We investigated the differences between the action of haloperidol and pimozide on dopamine metabolism and on catalepsy in periods up to 6 weeks after cessation of chronic administration of the neuroleptics to male Wistar rats. Dopamine and its metabolites (dihydroxyphenylacetic and homovanillic acids) were measured, using high-performance liquid chromatography (HPLC), in the frontal cortex, nucleus accumbens, and striatum. Both neuroleptics produced similar effects after a single dose: catalepsy and an increase of dopamine metabolism in the brain structures. However, haloperidol and pimozide differed after chronic treatment. In haloperidol-treated rats hypersensitivity of the dopaminergic system developed at the end of 2 weeks' administration, as evidenced by depression of dopamine metabolism. The biochemical changes were accompanied by behavioral hyperactivity that lasted up to 3 weeks. Dopamine metabolism in rats treated with pimozide was normal from 24 h after the end of the treatment, while catalepsy was maintained at the high level for up to 8 days and was observable up to 3 weeks after the last dose. Our results suggest that in contrast to haloperidol, pimozide is not able to produce adaptive changes leading to supersensitivity of the dopaminergic system. This may be the consequence of its potent Ca^{2+} channel blocking action.

Keywords: Haloperidol; Pimozide; (Chronic treatment); Dopamine metabolism; Catalepsy; Adaptation

1. Introduction

The primary action of neuroleptics was believed to be the blockade of dopamine D_2 receptors (Seeman et al., 1976). Recently, with the description of new subtypes of dopamine receptors, it was questioned whether the action on D_3 or D_4 receptors is the most important for their antipsychotic action (Seeman and Van Tol, 1993; Freedman et al., 1994), but extrapyramidal effects including catalepsy are probably dependent on dopamine D_2 receptors localized in the striatum (Hess et al., 1988). Also, the effects of neuroleptics on dopamine metabolism seem to be mediated chiefly by presynaptic D_2 receptors that control dopamine release (Cessalet, 1984; Nowak et al., 1990).

Haloperidol and pimozide are both regarded as effective typical neuroleptics, although the latter is much less investigated and less used in clinical practice. The two drugs belong to different chemical groups and show several differences, including their clinical action. Pimozide, a diphenylbutylpiperidine derivative, and haloperidol, a butyrophenone, are both antagonists of dopamine D_2 receptors, and bind equally to dopamine D_2 and D_3 receptors (Freedman et al., 1994). However, more recent studies show differences in their affinity for other receptors. Thus, pimozide is an effective antagonist of various types of 5-HT receptor, particularly the recently cloned rat 5-HT_7 receptor, to which it has the highest affinity ($K_i = 0.5$ nM) of all the typical antipsychotic agents, and is approximately 500 times more potent than haloperidol (Roth et al., 1994). Pimozide is also much more potent than haloperidol as an inhibitor of voltage-dependent Ca^{2+} channels (Antkiewicz-Michaluk et al., 1995) and calmodulin blocker (Weiss et al., 1982). In the clinic pimozide is regarded as an agent producing less tardive dyskinesia (McGuire et al., 1994) and is effective in combating not only positive, but also negative signs of schizophrenia (Feinberg et al., 1988).

Our earlier studies (Mamczarz et al., 1994; Antkie-

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wicz-Michaluk et al., 1995), in which we had systematically compared the effects of haloperidol and pimozide after a chronic treatment and short withdrawal period, demonstrated the essential differences in the behavioral and neurochemical profile of action of both neuroleptics. In this study we compare the effects of single and multiple doses of both neuroleptics during treatment and the withdrawal period on dopamine metabolism in the limbic and extrapyramidal structures of the rat brain; in parallel the cataleptic response evoked by the treatment was investigated.

2. Materials and methods

2.1. Animals and treatment

The experiments were carried out according to the Polish governmental regulations concerning experiments on animals (decree No. 71, art. 492 of December 28, 1959); the appropriate permission was granted.

The subjects were male Wistar rats, of initial weight 200–220 g, kept under standard laboratory conditions, 8 to a large animal cage (55 × 35 × 25 cm), with free access to standard laboratory food and tap water, at room temperature (approximately 22°C) with a natural day-night cycle (March–May). The experiments were carried out between 09:00 h and 14:00 h.

2.1.1. Drugs

Haloperidol (Sigma), 1 mg/kg, and pimozide (RBI), 4 mg/kg, were administered intraperitoneally (i.p.) as a suspension in 1% Tween 80 in a single dose or once daily for 14 days. The controls received the vehicle in a volume of 4 ml/kg.

2.1.2. Experimental schedule

Separate groups were tested for catalepsy and for changes in dopamine metabolism in the brain areas. The tests for catalepsy were carried out 90 min after the first, seventh and 14th day of chronic drug administration and in various periods during withdrawal (24 h to 6 weeks after the end of the chronic treatment). For biochemical assays the animals were killed 90 min after a single dose, and 24 h, 9 days and 6 weeks after the end of the chronic treatment.

2.2. Preparation of samples and chromatographic assay of dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA)

Dopamine and its metabolites were assayed by means of high-performance liquid chromatography (HPLC) in the frontal cortex, nucleus accumbens and striatum. Immediately after decapitation with a guillotine the brains were excised and dissected on an ice-chilled glass plate. The tissues were kept in dry ice until used.

The tissue samples were weighed and homogenized in ice-cold 0.1 M trichloroacetic acid containing 0.05 mM ascorbic acid. After centrifugation (10 000 × g, 5 min), the supernatants were filtered through RC 58 0.2 μm cellulose membranes (Bioanalytical Systems, West Lafayette, IN, USA), and dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were determined by HPLC with electrochemical detection. A BAS-400 liquid chromatograph was equipped with a 7 μm ODS guard column and 3 μm Phase-2 ODS cartridge column (100 × 3.2 mm). The mobile phase consisted of 0.05 M citrate-phosphate buffer, pH 3.5, 0.1 mM EDTA, 1 mM sodium octyl sulfonate and 3.5% methanol. The flow rate was maintained at 0.8 ml/min. Dopamine and its metabolites were quantified by peak height comparisons with standards run on the day of analysis with a sensitivity of 10–100 pg.

2.3. Catalepsy

The catalepsy was measured according to the method of Delini-Stula and Morpurgo (1968) as modified by Vetulani (1973). The rats were tested for their ability to maintain the unnatural posture (left or right forepaw on a 3 and 9 cm high wooden block) for 15 s. The maximum score was 6.

2.4. Statistics

The results were analyzed by means of one-way analysis of variance followed, when appropriate, with Fisher's Least Significant Difference test.

3. Results

3.1. Dopamine metabolism

3.1.1. Single dose

The effects of a single dose of haloperidol and pimozide were essentially similar and consisted of an increase in the concentrations of dopamine metabolites and in the dopamine/metabolite ratio, indicating an increased dopamine metabolism. At the given doses the effects of haloperidol in the dopamine-rich areas (nucleus accumbens and striatum) were approximately twice as large than those of pimozide. In the cortex a much weaker elevation of dopamine metabolites was observed and the effects of both neuroleptics were similar (Table 1).

3.1.2. Chronic treatment

Given chronically for 14 days, haloperidol and pimozide affected dopamine metabolism differently. In con-

Table 1
The effect of a single injection of haloperidol and pimozide on dopamine metabolism in rat brain structures

	Dopamine		DOPAC			HVA		
	ng/g tissue (*n*)	%	ng/g tissue (*n*)	%	*f*	ng/g tissue (*n*)	%	*f*
Cortex								
Control	369 ± 47 (11)	100	75 ± 10 (11)	100	20	79 ± 17 (11)	100	21
Haloperidol	398 ± 44 (6)	108	105 ± 13 (5)	140	26	216 ± 33 (5) [b]	273	54
Pimozide	335 ± 41 (5)	91	146 ± 11 (5) [b]	194	43	113 ± 13 (5)	143	33
Nucleus accumbens								
Control	12736 ± 988 (10)	100	1622 ± 99 (10)	100	12	876 ± 81 (10)	100	7
Haloperidol	13150 ± 414 (5)	103	5647 ± 357 (5) [b]	348	43	3765 ± 422 (5) [b]	430	29
Pimozide	9318 ± 919 (5) [a]	73	2921 ± 349 (5) [a]	180	31	1692 ± 224 (5) [a]	193	18
Striatum								
Control	8780 ± 560 (12)	100	1074 ± 58 (12)	100	12	791 ± 47 (12)	100	9
Haloperidol	8200 ± 914 (6)	93	4348 ± 155 (6) [b]	405	53	3313 ± 170 (6) [b]	419	40
Pimozide	8766 ± 754 (5)	99	2665 ± 125 (5) [b]	248	30	2283 ± 113 (5) [b]	288	26

The rats were killed 90 min after injection of the neuroleptics: haloperidol (1 mg/kg i.p.) and pimozide (4 mg/kg i.p.). The concentrations (ng/g tissue) are means ± S.E.M. (*n*). *f* = metabolite ratio ([metabolite]/[dopamine]) × 100. [a] $P < 0.05$, [b] $< P < 0.01$ (difference from control, Dunnett's test).

trast to the effect of a single dose, chronic haloperidol in all the investigated structures depressed dopamine metabolism, as evidenced by a significant decrease in the levels of dopamine metabolites and in the dopamine/metabolite ratio.

The dopamine metabolism in rats given pimozide chronically was essentially unchanged in comparison with that of the control (Table 2).

3.1.3. Withdrawal period

After 9 days of withdrawal from the chronic treatment with haloperidol, dopamine metabolism was still significantly depressed in the striatum (both metabolites) and in the nucleus accumbens (HVA). The metabolite/dopamine ratios were still lower after haloperidol withdrawal, even in the cortex, in which the changes in metabolite levels did not reach the level of significance. However, the depression of dopamine metabolism was smaller than that observed immediately at the end of the treatment.

The pimozide-treated rats still showed an insignificant tendency to an increase in metabolite levels in the cortex, while in other structures metabolite levels and metabolite ratios did not differ from those of control (Table 3).

Six weeks after the end of chronic treatment generally

Table 2
The effect of chronic administration of haloperidol and pimozide on dopamine metabolism in rat brain structures

	Dopamine		DOPAC			HVA		
	ng/g tissue (*n*)	%	ng/g tissue (*n*)	%	*f*	ng/g tissue (*n*)	%	*f*
Cortex								
Control	289 ± 11 (16)	100	83 ± 4 (16)	100	29	90 ± 6 (16)	100	31
Haloperidol	326 ± 47 (6)	113	60 ± 7 (6) [a]	72	18	48 ± 4 (6) [b]	53	15
Pimozide	299 ± 27 (5)	103	98 ± 14 (5)	118	33	79 ± 11 (6)	88	27
Nucleus accumbens								
Control	10568 ± 509 (16)	100	1621 ± 93 (20)	100	15	758 ± 36 (20)	100	7
Haloperidol	10676 ± 927 (6)	101	1171 ± 121 (6) [a]	72	11	419 ± 59 (6) [b]	55	4
Pimozide	10511 ± 590 (6)	99	1923 ± 127 (6)	118	18	847 ± 106 (6)	112	8
Striatum								
Control	9850 ± 387 (24)	100	1200 ± 53 (18)	100	12	778 ± 37 (22)	100	8
Haloperidol	9164 ± 570 (5)	92	794 ± 31 (5) [b]	66	9	340 ± 26 (5) [b]	43	4
Pimozide	8778 ± 582 (5)	89	1217 ± 128 (5)	101	14	714 ± 63 (5)	92	8

The rats were killed 24 h after the last injection of the neuroleptics given daily for 14 days: haloperidol (1 mg/kg i.p.) and pimozide (4 mg/kg i.p.). The concentrations (ng/g tissue) are means ± S.E.M. (*n*). *f* = metabolite ratio ([metabolite]/[dopamine]) × 100. [a] $P < 0.05$, [b] $< P < 0.01$ (difference from control, Dunnett's test).

Table 3
The effect of 9 days' withdrawal from chronic administration of haloperidol and pimozide on dopamine metabolism in rat brain structures

	Dopamine		DOPAC			HVA		
	ng/g tissue (*n*)	%	ng/g tissue (*n*)	%	*f*	ng/g tissue (*n*)	%	*f*
Cortex								
Control	289 ± 11 (16)	100	83 ± 4 (16)	100	29	90 ± 6 (16)	100	31
Haloperidol	447 ± 39 (6) [b]	155	81 ± 11 (6)	97	18	62 ± 10 (6)	69	14
Pimozide	282 ± 25 (6)	97	95 ± 8 (6)	114	33	104 ± 13 (6)	115	37
Nucleus accumbens								
Control	10568 ± 509 (16)	100	1621 ± 93 (20)	100	15	758 ± 36 (20)	100	7
Haloperidol	11955 ± 771 (6)	113	1362 ± 120 (6)	84	11	549 ± 33 (6) [b]	72	4
Pimozide	9613 ± 296 (6)	91	1483 ± 105 (6)	92	15	750 ± 53 (6)	99	7
Striatum								
Control	9850 ± 387 (24)	100	1200 ± 53 (18)	100	12	778 ± 37 (22)	100	8
Haloperidol	8602 ± 490 (6)	87	887 ± 55 (6) [b]	74	10	433 ± 51 (6) [b]	55	5
Pimozide	8493 ± 364 (6)	86	1042 ± 96 (6)	87	12	678 ± 36 (6)	87	8

The rats were killed 9 days after the last injection of the neuroleptics given daily for 14 days: haloperidol (1 mg/kg i.p.) and pimozide (4 mg/kg i.p.). The concentrations (ng/g tissue) are means ± S.E.M. (*n*). *f* = metabolite ratio ([metabolite]/[dopamine]) × 100. [a] $P < 0.05$, [b] $< P < 0.01$ (difference from control, Dunnett's test).

no neuroleptic-induced changes persisted. Not only the metabolite concentration, but also the metabolite ratios were similar in all groups. The only change, which also did not reach significance, was a decrease (by over 30%) of DOPAC level in the cortex after both neuroleptics (Table 4).

3.2. Catalepsy

A single dose of both neuroleptics produced moderate catalepsy 90 min after the injection. The catalepsy was much stronger, although still submaximal, after the last dose of the multiple treatment. The difference between haloperidol and pimozide was very pronounced during the

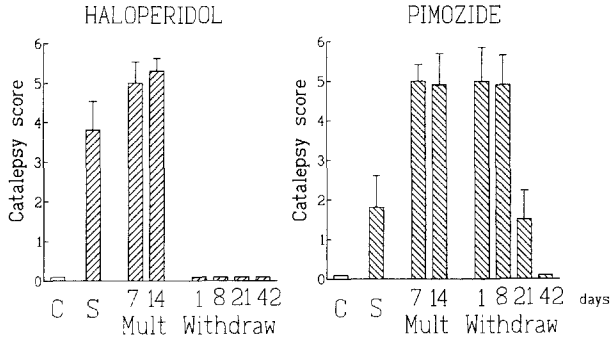

Fig. 1. Neuroleptic-induced catalepsy after a single or multiple doses and during withdrawal. C: control, S: 90 min after a single dose, Mult: multiple dose treatment (90 min after 7th and 14th dose), Withdraw: on the 1st, 8th, 21st and 42nd day after the last dose. The bars represent means + S.E.M. of 12 (treatment) or 8 (withdrawal) results.

Table 4
The effect of 6 weeks' withdrawal from chronic treatment with haloperidol and pimozide on dopamine metabolism in rat brain structures

	Dopamine		DOPAC			HVA		
	ng/g tissue (*n*)	%	ng/g tissue (*n*)	%	*f*	ng/g tissue (*n*)	%	*f*
Cortex								
Control	340 ± 23 (6)	100	66 ± 13 (6)	100	19	62 ± 6 (5)	100	18
Haloperidol	253 ± 38 (6)	74	48 ± 6 (6)	73	19	57 ± 12 (5)	92	22
Pimozide	312 ± 38 (6)	92	44 ± 9 (6)	67	14	62 ± 6 (5)	100	20
Nucleus accumbens								
Control	10039 ± 555 (6)	100	1389 ± 7 (6)	100	14	598 ± 31 (6)	100	6
Haloperidol	10189 ± 567 (6)	101	1297 ± 105 (6)	93	13	597 ± 67 (6)	99	6
Pimozide	10533 ± 959 (6)	105	1434 ± 163 (6)	103	14	714 ± 98 (6)	119	7
Striatum								
Control	11482 ± 603 (6)	100	954 ± 22 (6)	100	8	654 ± 61 (6)	100	6
Haloperidol	9618 ± 329 (6)	84	1013 ± 65 (6)	106	10	508 ± 38 (6)	77	5
Pimozide	10546 ± 523 (6)	92	798 ± 43 (6)	84	8	512 ± 49 (6)	78	5

The rats were killed 6 weeks after the last injection of the neuroleptics given daily for 14 days: haloperidol (1 mg/kg i.p.) and pimozide (4 mg/kg i.p.). The concentrations (ng/g tissue) are means ± S.E.M. (*n*). *f* = metabolite ratio ([metabolite]/[dopamine]) × 100. [a] $P < 0.05$, [b] $< P < 0.01$ (difference from control, Dunnett's test).

withdrawal period: while after treatment with haloperidol the catalepsy disappeared within 24 h, and the rats were hyperresponsive to touch and overreactive, in pimozide-treated rats catalepsy remained on the same high level for at least 8 days and was still present after 3 weeks of withdrawal (Fig. 1).

4. Discussion

The present results confirm that haloperidol and pimozide have a different profile of action after chronic treatment. Single doses of both neuroleptics produced similar effects, characteristic for classical neuroleptics: a marked catalepsy and a potent increase in the accumbens and striatal levels of the dopamine metabolites, DOPAC and HVA. The catalepsy reflects the blockade of striatal dopamine receptors while the biochemical changes may be interpreted as a rapid feedback response to dopamine receptor blockade (Van Rossum, 1967). The investigation of the effects after chronic treatment suggests that haloperidol and pimozide differently affect the adaptive changes of dopamine receptors. The chronic dopamine receptor blockade induced by neuroleptics leads to an adaptive response consisting of functional hypersensitivity of dopaminergic system, as evidenced by increased responsiveness to dopamine receptor agonists (Burt et al., 1977; Muller and Seeman, 1978; Fleminger et al., 1983; MacKenzie and Zigmond, 1985) and suppression of dopamine metabolism (Clow et al., 1980). Our former (Antkiewicz-Michaluk et al., 1995) and present results with haloperidol confirm the earlier data. As demonstrated now, this supersensitivity could not prevent the cataleptic effect of haloperidol shortly after the last of the multiple doses, but the drug treatment produced behavioral hyperactivity within 24 h after the last dose, although at this time haloperidol is still present in brain (Statford et al., 1984). This behavioral compensatory response was accompanied by biochemical changes indicative of suppression of dopamine metabolism. The metabolic changes were still present after 9 days, and in our former experiments (Mamczarz et al., 1994; Antkiewicz-Michaluk et al., 1995) we have observed in this period of withdrawal that the hyperreactivity and hyperresponsiveness to dopamine agonists is paralleled by an increase in dopamine receptor density.

The chronic administration of pimozide produced much fewer adaptive changes in dopamine metabolism and no such changes in animal behavior. Dopamine metabolism 24 h after chronic treatment did not differ significantly from normal levels, and in all structures the mean concentrations of both DOPAC and HVA were consistently higher than in the controls. Only after 9 days of withdrawal were the biochemical parameters in the control and pimozide-treated group the same, and suppression of dopamine metabolism was never observed. The behavioral observations showed that sedation and catalepsy are almost unchanged for the period up to 9 days after withdrawal, and some effects of this type are visible even after 3 weeks. In no case was hyperactivity or any other sign of supersensitivity observed long after cessation of pimozide. Our earlier studies (Antkiewicz-Michaluk et al., 1995) demonstrated that the response to apomorphine was still suppressed 9 days after pimozide withdrawal.

Summing up, our results indicate that despite the similar receptor profile of action of haloperidol and pimozide (Janssen et al., 1968; Hyttel et al., 1985) the two drugs induce different, and even opposite, effects upon chronic treatment and withdrawal. The difference may be interpreted in terms of the different ability of haloperidol and pimozide to produce adaptive changes in the dopaminergic system. The dopaminergic system adapts rapidly to blockade induced by haloperidol, and because of this it shows signs of hypercompensation after withdrawal of the drug. In the case of chronic treatment with pimozide, the adaptation of the dopaminergic system is very limited. Because of this no signs of hypercompensation appear in biochemical parameters, and behaviorally the neuroleptic action is maintained for some time after withdrawal.

The reason for the difference in adaptation to haloperidol and to pimozide is not clear yet. Based on our previous results, in which we observed that behavioral effects during withdrawal from haloperidol co-administered with a Ca^{2+} channel blocker, nifedipine, resembled those observed during pimozide withdrawal (Antkiewicz-Michaluk et al., 1995; Mamczarz et al., 1994), we assume that the difference between pimozide and haloperidol may result from different effects of the two neuroleptics on Ca^{2+} metabolism. Pimozide is much more potent than haloperidol as a blocker of voltage-dependent Ca^{2+} channels (Gould et al., 1983; Enyeart et al., 1990) and of calmodulin activity (Weiss et al., 1982; Izosaki et al., 1994). In our experiments the potency of pimozide as a displacing agent of [^{3}H]nitrendipine was comparable with that of the classical Ca^{2+} channel antagonist nifedipine, while haloperidol was 100 times less potent in this respect (Antkiewicz-Michaluk et al., 1995). As the functional state of Ca^{2+} channels is critical for the development of adaptive changes (Antkiewicz-Michaluk et al., 1993), this may explain the fact that the action of pimozide, in contrast to that of haloperidol, does not change its direction after chronic treatment and during withdrawal. However, our preliminary results suggest that nifedipine co-administration does not prevent the effects of haloperidol on dopamine metabolism during withdrawal. This does not necessarily rule out the involvement of Ca^{2+} in the action of pimozide: the metabolic changes are due to a presynaptic action of neuroleptics, and N-type Ca^{2+} channels, which are not sensitive to dihydropyridines, are the main Ca^{2+} channels at nerve terminals (Miller, 1987). It should also be mentioned that calmodulin plays an important role in presynaptic mechanisms, and pimozide is a much more

potent calmodulin inhibitor than haloperidol (Weiss et al., 1982; Izosaki et al., 1994). It is also possible that another striking difference between pimozide and haloperidol – the very potent binding of the former to 5-HT_7 receptors (Roth et al., 1994) – may be important for the differences in the action of the two neuroleptics. However, no data indicating an interaction of 5-HT_7 receptors and dopamine neurons are presently available.

It might be speculated that pimozide produces only mild adaptive changes because of its Ca^{2+} channel and/or calmodulin blocking properties. Regardless of the mechanisms preventing the dopaminergic system from adapting rapidly to pimozide, because of the attenuation of adaptive responses, the effects characteristic for a single dose of the neuroleptic disappear smoothly during the chronic treatment, and no hypercompensation phase appears. The lack of propensity to induce hypercompensation may explain the fact that pimozide does not produce signs of tardive dyskinesia (McGuire et al., 1994). The question remains whether the inhibitory action of pimozide on Ca^{2+} metabolism or on 5-HT_7 receptors is related to its beneficial action on negative signs of schizophrenia (Opler and Feinberg, 1991), which are not effectively relieved by haloperidol and most of the classic neuroleptics.

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References

Antkiewicz-Michaluk, L., J. Michaluk, I. Romañska and J. Vetulani, 1993, Reduction of morphine dependence and potentiation of analgesia by chronic co-administration of nifedipine, Psychopharmacology 111, 457.

Antkiewicz-Michaluk, L., B. Karolewicz, J. Michaluk and J. Vetulani, 1995, Differences between haloperidol and pimozide-induced withdrawal syndrome: a role for Ca^{2+} channels, Eur. J. Pharmacol. 294, 459.

Burt D.R., I. Creese and S.H. Snyder, 1977, Antischizophrenic drugs: chronic treatment elevates dopamine receptor binding in the brain, Science 196, 326.

Cessalet, M.F., 1984, Presynaptic regulation of neurotransmitter release in the brain: facts and hypothesis, Neuroscience 12, 347.

Clow, A., A. Theodorou, P. Jenner, C.D. Marsden, 1980, Changes in rat striatal dopamine turnover and receptor activity during one year neuroleptic administration, Eur. J. Pharmacol. 63, 135.

Delini-Stula, A. and C. Morpurgo, 1968, Influence of amphetamine and scopolamine on the catalepsy induced by diencephalic lesions in rats, Int. J. Neuropharmacol. 7, 391.

Enyeart, J.J., R.T. Dirksen, V.K. Sharma, D.J. and S.S. Sheu, 1990, Antipsychotic pimozide is a potent Ca^{2+} channel blocker in heart, Mol. Pharmacol. 37, 752.

Feinberg, S.S., S.R. Kay, L.R. Elijovich, A. Fiszbein and L.A. Opler, 1988, Pimozide treatment of the negative schizophrenic syndrome: an open trial, J. Clin. Psychiatry 49, 235.

Fleminger, S., N.M.J. Rupniak, M.D. Hall, P. Jenner, C.D. Marsden, 1983, Changes in apomorphine-induced stereotypy, as a result of subacute neuroleptic treatment, correlates with increased D-2 receptor but not increases in D-1 receptors, Biochem. Pharmacol. 32, 2921.

Freedman, S.B., S. Patel, R. Marwood, F. Emms, G.R. Seabrook, M.R. Knowles and G. McAllister, 1994, Expression and pharmacological characterization of the human D_3 dopamine receptor, J. Pharmacol. Exp. Ther. 268, 417.

Gould, R.J., K.M.M. Murphy, I.J. Reynolds and S.H. Snyder, 1983, Antischizophrenic drugs of the diphenylbutylpiperidine type act as calcium channel antagonist, Proc. Natl. Acad. Sci. USA, 80, 5122.

Hess, E.J., A.B. Norman and J. Creese, 1988, Chronic treatments with dopamine receptor antagonists: Behavioral and pharmacological effects on D_1 and D_2 dopamine receptors, J. Neurosci. 8, 2361.

Hyttel, J., J.J. Larsen, A.V. Christensen and J. Arnt, 1985, Receptor binding profiles of neuroleptics, in: Dyskinesia. Research and Treatment, Psychopharmacology, Suppl. 2, 9.

Izosaki, M., N. Minami and T. Nakashima, 1994, Pharmacological evidence for regulation of Na(+)-Ca(++) exchange by calcium/calmodulin-dependent protein kinase in isolated bovine adrenal medullary cells, J. Pharmacol. Exp. Ther. 270, 104.

Janssen, P.A.J., C.J.E. Niemegeers K.H.L. Schellenkens, A. Dresse, M.F. Leanerts, A. Pinchard, W.K.A. Schaper, J.M. Van Nueten and F.J. Verruggen, 1968, Pimozide, a chemically novel, highly potent and orally long-acting neuroleptic drug, Arzneim.-Forsch. 18, 261.

MacKenzie, R.G., M.J. Zigmond, 1985, Chronic neuroleptic treatment increases D-2 but not D-1 receptors in rat striatum, Eur. J. Pharmacol. 113, 159.

Mamczarz, J., B. Karolewicz, L. Antkiewicz-Michaluk and J. Vetulani, 1994, Co-administration of nifedipine with neuroleptics prevents development of activity changes during withdrawal, Pol. J. Pharmacol. 46, 75.

McGuire, B.E., E. Akuffo and G.L. Choon, 1994, Somatic sexual hallucinations and erotomanic delusions in a mentally handicapped woman, J. Intellect. Disabil. Res. 38, 79.

Miller, R., 1987, Multiple calcium channels and neuronal function, Science 235, 46.

Muller, P. and P. Seeman, 1978, Dopaminergic supersensitivity after neuroleptics: time course and specificity, Psychopharmacology 60, 1.

Nowak, J.Z., S. Arbilla, S.G. Dahl and S.Z. Langer, 1990, Antagonism of presynaptic dopamine receptors by phenothiazine drug metabolites, Life Sci. 46, 443.

Opler, L.A. and S.S. Feinberg, 1991, The role of pimozide in clinical psychiatry: a review, J. Clin. Psychiatry 52, 221.

Roth, B.L., S.C. Craigo, M.S. Choudhary, A. Uluer, F.J. Monsma, J.Y. Shen, H.Y. Meltzer and D.R. Sibley, 1994, Binding of typical and atypical antipsychotic agents to 5-hydroxytryptamine-6 and 5-hydroxytryptamine-7 receptors, J. Pharmacol. Exp. Ther. 268, 1403.

Seeman, P. and H.M. Van Tol, 1993, Dopamine D_4 receptors bind inactive (+)-aporphines, suggesting neuroleptic role. Sulpiride not stereoselective, Eur. J. Pharmacol. 233, 173.

Seeman, P., T. Lee, M. Chan-Wong and K. Wong, 1976, Antipsychotic drug doses and neuroleptic/dopamine receptors, Nature 261, 717.

Statford, J.E., L.S. Jackson, T.J. Forrest, A. Barrow and R.F. Palmer, 1984, Haloperidol pharmacokinetics: a preliminary study in rhesus monkeys using a new radioimmunoassay procedure, J. Pharmacol. Methods 6, 261.

Van Rossum, J.M., 1967, The Significance of Dopamine Receptor Blockade for the Action of Neuroleptic Drugs, Neuro-Psycho-Pharmacology, ed. H. Brill (Excerpta Medica, Amsterdam) p. 321.

Vetulani, J, 1973, The action of neuroleptics in rats with altered catecholamine metabolism. Part I. The influence of MAO inhibitors on the behavioral actions of chlorpromazine, haloperidol and thioridazine, Pol. J. Pharmacol. Pharm. 25, 41.

Weiss, B., W.C. Prozialeck and T.L. Wallace, 1982, Interaction of drugs with calmodulin. Biochemical, pharmacological and clinical implications, Biochem. Pharmacol. 31, 2217.