Indian J Physiol Pharmacol 1999; 43 (1) : 44–52

EFFECTS OF VERAPAMIL ON DOPAMINE DEPENDENT BEHAVIOURS IN RATS

A. R. MALEKAR, J. J. BALSARA* AND R. K. GAONKAR

Department of Pharmacology,
Krishna Institute of Medical Sciences,
Karad – 415 110

(Received on April 23, 1998)

Abstract : Verapamil at 5, 10 and 20 mg/kg ip did not inhibit the conditioned avoidance response, neither induced catalepsy nor antagonised apomorphine stereotypy in rats indicating that these doses do not block the postsynaptic striatal D 2 and D 1 dopamine (DA) receptors. However, pretreatment with 10 and 20 mg/kg ip verapamil potentiated methamphetamine stereotypy and antagonised catalepsy induced by small doses (0.05 and 0.1 mg/kg ip) of apomorphine. Antagonism of small dose apomorphine-induced catalepsy suggests that at these doses verapamil blocks the presynaptic D2 DA autoreceptors. Further, pretreatment with 10 mg/kg verapamil antagonised, while pretreatment with 20 mg/kg potentiated haloperidol catalepsy. Potentiation of methamphetamine stereotypy by 10 and 20 mg/kg verapamil is explained on the basis of blockade of presynaptic D2 DA autoreceptors by these doses of verapamil and its reported DA neuronal uptake blocking activity. Antagonism of haloperidol catalepsy by 10 mg/kg verapamil is also explained on the basis of presynaptic D2 DA autoreceptor induced blockade by 10 mg/kg verapamil whereas potentiation of haloperidol catalepsy by 20 mg/kg verapamil is explained on the basis of its calcium channel blocking activity.

Key words : verapamil, haloperidol, apomorphine, methamphetamine, stereotypy, catalepsy, conditioned avoidance, response, rat

INTRODUCTION

Verapamil competitively inhibits ^{3}H–spiperone binding to D2 dopamine (DA) receptors in homogenates of the rat corpus striatum (1), facilitates the intraneuronal inactivation of vesicular DA in rat striatal and olfactory synaptosomes (2) and decreases the levels of the DA metabolite 3, 4 dihydroxyphenylacetic acid in the rat brain without changing the levels of homovanillic acid, indicating that it decreases the synthesis of DA (3). Further, Tsuda et al (4) have reported that verapamil increases both basal and electrically stimulated ^{3}H DA release in rat striatal slices and antagonises the inhibitory effect of unlabelled exogenously applied DA on stimulation-evoked ^{3}H DA release, indicating thereby that verapamil exerts

*Corresponding Author

presynaptic D 2 DA autoreceptor blocking activity. As the cited reports indicate that verapamil can influence the activity of the central dopaminergic systems we have therefore investigated the effect of verapamil treatment on DA–dependent behaviours in rats.

METHODS

Male albino rats weighing between 100 to 180 g were used for the study. They were allowed food and water ad libitum. Animals were randomly distributed into groups of 10 animals each. Each animal was used only once. All observations were made between 10 and 16 h at 27–30° C in a noiseless diffusely illuminated room. Observations were made by an experimenter who was unaware of the animal's treatment.

Verapamil HCl (Courtesy, Torrent Pharmaceutical Ltd India) was dissolved in 2% solution of Tween 80 in distilled water while apomorphine HCl (Sigma U.S.A.) was dissolved in distilled water containing 0.2 mg/ml ascorbic acid. Methamphetamine HCl (Courtesy Burroughs Wellcome Ltd.) and haloperidol (Courtesy Searle) injection solutions were diluted to required strength with distilled water. Doses refer to the forms mentioned. All drug solutions were prepared immediately before use and were injected intraperitoneally in a volume not exceeding 0.4 ml/100 g body weight.

Conditioned avoidance response (CAR) in rats : The effect on CAR was studied in trained rats by the technique of Cook and Weidley (5), using Cook's pole climbing response apparatus. The animals were trained for the acquisition of CAR as follows. Each rat, in turn, was placed in the test chamber for a period of 30 s, without any stimulus, to allow adaptation to the new environment. Then a series of electric foot shocks (80 volts, 5 pulses/sec) were delivered through the grid floor with simultaneous ringing of the buzzer for 30 s or until the rat managed to climb the pole to escape the shock (unconditioned escape response to the electric shock). The rats were trained 3 times a day for 3 days. On the fourth day, rats were exposed to the sound of buzzer only. Rats climbing the pole within 30s of being exposed to the buzzer sound were considered to have acquired the CAR and the rats showing this response on a stable basis were used for further studies. On the day of the experiment the animal had to make 3 consecutive correct avoidance responses prior to drug (verapamil or haloperidol) or vehicle administration. The rats were retested for CAR 1h after the administration of verapamil (5, 10 and 20 mg/kg), haloperidol (0.5 mg/kg) or vehicle. The drug and vehicle treatment effect on CAR was expressed as the percentage of animals which failed to climb the pole within 30s of being exposed to the buzzer sound but did climb the pole within 30s in response to the subsequently delivered electric foot shocks.

Apomorphine and methamphetamine induced stereotyped behaviour (SB) in rats : The rats were placed in individual cages made of wire netting, measuring 30 × 20 × 20 cm, 30 min before drug or vehicle treatment to allow adaptation. The intensity of SB was assessed over a 30s observation period at 10 min intervals throughout its duration, using the scoring system of Costall and Naylor (6) where

periodic sniffing = score 1, continuous sniffing = 2, periodic biting, gnawing or licking = 3 and continuous biting, gnawing or licking = 4. The maximum intensity of SB scored by each rat in the group was taken to compute the mean value of the group. Verapamil (5, 10 and 20 mg/kg) or haloperidol (0.5 mg/kg) was injected 1h before apomorphine or methamphetamine while the control groups received the requisite vehicle (Tween 80 or distilled water) 1h before receiving the DA agonists.

Induction of catalepsy in rats : Rats were tested for catalepsy according to the method of Costall and Naylor (6) by placing both front limbs of the animal over an 8 cm high wooden block and measuring the time that the animal maintained the imposed posture. Animals maintaining the imposed posture for more than 10s were considered to be cataleptic. Animals were tested for catalepsy 0.5, 1, 2, 3 and 4h after ip injection of verapamil, haloperidol, Tween 80 or distilled water.

Catalepsy induced by haloperidol and small doses of apomorphine in rats : Verapamil was injected 1h before haloperidol (0.5, and 1 mg/kg) or small doses of apomorphine (0.05 and 0.1 mg/kg). Control groups received 0.4 ml/100 g ip of 2% solution of Tween 80 1h before receiving haloperidol or apomorphine. Animals were evaluated for catalepsy. 1 and 2h after haloperidol or apomorphine treatment. Scoring, modified from that of Costall and Naylor (6) was as follows : maintaining the imposed posture 0–10s (0.), 11–30s (1); 31–60s (2); 61–120s (3); 121s and more (4). Catalepsy score of each animal in the group, at the respective testing time interval, was taken to compute the mean value of the group for that particular timing.

The results were analysed by the non-parametric Mann-Whitney U–test with differences considered significant at $P<0.05$.

RESULTS

The solvent Tween 80 (0.4 ml/100g ip of 2% solution in distilled water) and verapamil (5, 10 and 20 mg/kg ip) did not produce motor incoordination, ataxia or muscular hypotonia, neither did they stimulate locomotor activity or induced stereotyped behaviour in the rats. The animals appeared the same as distilled water treated controls. Doses of verapamil beyond 20 mg/kg produced motor incoordination, ataxia, muscular hypotonia and mortality, hence were not used in the present study.

1. Effect on CAR in rats : Treatment with verapamil (5, 10 and 20 mg/kg), Tween 80 and distilled water did not inhibit the CAR and the unconditioned escape response (UER) to the electric shock. Haloperidol (0.5 mg/kg) selectively inhibited the CAR in 100% of the animals without inhibiting the UER to the electric shock.

2. Effect on apomorphine induced SB in rats : Apomorphine (0.5, 1 and 2 mg/kg induced dose-dependent SB which had a rapid onset, within 10 min of injection, and lasted for about 30 to 45 min. Pretreatment with 5, 10 and 20 mg/kg verapamil did not significantly influence apomorphine stereotypy (Table I). However, pretreatment with 0.5 mg/kg haloperidol abolished the SB induced by 0.5, 1 and 2 mg/kg apomorphine (Table I).

TABLE I : Effect of verapamil (VER) and haloperidol (HAL) pretreatment on apomorphine (APO) induced stereotyped behaviour in rats.

Study	*Group (n=10)*	*Treatment (mg/kg, ip)*	*Intensity Score (Mean ± SEM)*
I. A.	1.	TW + APO (0.5)	1.1±0.10
	2.	VER (5) + APO (0.5)	1.2±0.13
	3.	VER (10) + APO (0.5)	1.0±0.00
	4.	VER (20) + APO (0.5)	1.3±0.15
B.	1.	DW + APO (0.5)	1.2±0.13
	2.	HAL (0.5) + APO (0.5)	0.0
II. A.	1.	DW + APO (1)	2.2±0.13
	2.	VER (5) + APO (1)	2.3±0.15
	3.	VER (10) + APO (1)	2.1±0.10
	4.	VER (20) + APO (1)	2.3±0.15
B.	1.	DW + APO (1)	2.1±0.10
	2.	HAL (0.5) + APO (1)	0.0
III. A.	1.	DW + APO (2)	3.3±0.15
	2.	VER (5) + APO (2)	3.2±0.13
	3.	VER (10) + APO (2)	3.4±0.16
	4.	VER (20) + APO (2)	3.2±0.13
B.	1.	DW + APO (2)	3.2±0.13
	2.	HAL (0.5) + APO (2)	0.0

TW = Tween 80 (0.4 ml/100 g of 2% solution, ip);
DW = Distilled water (0.2 ml/100 g, ip).

TABLE II : Effect of verapamil (VER) and haloperidol (HAL) pretreatment on methamphetamine (MAM) induced stereotyped behaviour in rats.

Study	*Group (n=10)*	*Treatment (mg/kg, ip)*	*Intensity Score (Mean ± SEM)*
I. A.	1.	TW + MAM (4)	1.2±0.13
	2.	VER (5) + MAM (4)	1.6±0.16
	3.	VER (10) + MAM (4)	1.9±0.10*
	4.	VER (20) + MAM (4)	2.3±0.15**
B.	1.	DW + MAM (4)	1.1±0.10
	2.	HAL (0.5) + MAM (4)	0.0
II. A.	1.	DW + MAM (6)	3.0±0.00
	2.	VER (5) + MAM (6)	3.4±0.16
	3.	VER (10) + MAM (6)	3.7±0.15*
	4.	VER (20) + MAM (6)	4.0±0.00***
B.	1.	DW + MAM (6)	3.1±0.10
	2.	HAL (0.5) + MAM (6)	0.0

*P<0.05, **P<0.01, ***P<0.001 as compared to respective vehicle pretreated control methamphetamine group by Mann – Whitney's U – test.
TW = Tween 80 (0.4 ml/100 g of 2% solution, ip);
DW = Distilled water (0.2 ml/100 g. ip).

3. Effect on methamphetamine induced SB in rats : Methamphetamine (4 and 6 mg/kg) induced dose-dependent SB which, depending on the dose used, manifested about 10 to 20 min after the injection and lasted for about 2.5 to 3.5h. Pretreatment with 5 mg/kg verapamil did not significantly influence methamphetamine stereotypy. However, pretreatment with 10 and 20 mg/kg verapamil significantly increased the intensity of SB induced by 4 and 6 mg/kg methamphetamine while pretreatment with 0.5 mg/kg haloperidol abolished the SB induced by 4 and 6 mg/kg methamphetamine (Table II).

4. Induction of catalepsy in rats : Treatment with verapamil (5, 10 and 20 mg/kg), Tween 80 or distilled water did not induce catalepsy in rats at any of the testing time intervals. Haloperidol (1 mg/kg) induced catalepsy in 100% of the rats at all the testing time intervals.

5. Effect on haloperidol induced catalepsy in rats : Pretreatment with 5 mg/kg verapamil did not significantly affect the cataleptic effect of 0.5 and 1 mg/kg haloperidol at 1 and 2h testing time intervals. However, pretreatment with 10 mg/kg verapamil significantly decreased the cataleptic effect of 0.5 and 1 mg/kg haloperidol at both 1 and 2h testing time intervals while pretreatment with 20 mg/kg verapamil significantly increased the cataleptic effect of 0.5 and 1 mg/kg haloperidol at both 1 and 2h testing time intervals (Table III).

6. Effect on catalepsy induced by small doses of apomorphine in rats : The small doses of apomorphine (0.05 and 0.1 mg/kg ip) and the 1 and 2h testing time intervals after apomorphine administration used in the present study were based on the report of Balsara et al (7). Pretreatment with 5 mg/kg verapamil did not significantly affect the cataleptic effect of 0.05 and 0.1 mg/kg apomorphine at 1 and 2 h testing time intervals. However, pretreatment with 10 and 20 mg/kg, verapamil significantly decreased the cataleptic effect of 0.05 and 0.1 mg/kg apomorphine at both 1 and 2h testing time intervals (Table IV).

TABLE III : Effect of verapamil (VER) pretreatment on haloperidol (HAL) induced catalepsy in rats.

Study	*Group (n=10)*	*Treatment (mg/kg, ip)*	*Catalepsy Score (Mean ± SEM)* 1h	2h
I.	1.	TW + HAL (0.5)	1.9±0.10	1.7±0.15
	2.	VER (5) + HAL (0.5)	1.5±0.16	1.3±0.15
	3.	VER (10) + HAL (0.5)	1.1±0.10**	0.9±0.10**
	4.	VER (20) + HAL (0.5)	2.6±0.16*	2.4±0.16*
II.	1.	TW + HAL (1)	2.8±0.13	2.6±0.16
	2.	VER (5) + HAL (1)	2.4±0.16	2.2±0.13
	3.	VER (10) + HAL (1)	2.0±0.00**	1.8±0.13**
	4.	VER (20) + HAL (1)	3.5±0.16*	3.3±0.15*

*P<0.05, **P<0.01 as compared to respective vehicle pretreated control haloperidol group, at the respective testing time interval, by Mann – Whitney's U – test.
TW = Tween 80 (0.4 ml/100 g of 2% solution, ip).

TABLE IV : Effect of verapamil (VER) pretreatment on catalepsy induced by small doses of apomorphine (APO) in rats.

Study	*Group (n=10)*	*Treatment (mg/kg, ip)*	*Catalepsy Score (Mean ± SEM)* *1h*	*2h*
I.	1.	TW + APO (0.05)	1.6±0.16	1.8±0.13
	2.	VER (5) + APO (0.05)	1.2±0.13	1.4±0.16
	3.	VER (10) + APO (0.05)	0.9±0.10*	1.1±0.10*
	4.	VER (20) + APO (0.05)	0.6±0.16**	0.8±0.13**
II.	1.	TW + APO (0.1)	2.3±0.15	2.5±0.16
	2.	VER (5) + APO (0.1)	1.9±0.10	2.1±0.10
	3.	VER (10) + APO (0.1)	1.6±0.16*	1.8±0.13*
	4.	VER (20) + APO (0.1)	1.3±0.15**	1.5±0.16**

*P<0.05, **P<0.01 as compared to respective vehicle pretreated control apomorghine group, at the respective testing time interval, by Mann – Whitney's U – test.
TW = Tween 80 (0.4 ml/100 g of 2% solution, ip).

DISCUSSION

The D 2 DA receptor antagonists and the selective D 1 DA receptor antagonist SCH 23390, by blocking the postsynaptic striatal D 2 and D 1 DA receptors respectively, inhibit the CAR, antagonise apomorphine and amphetamine stereotypies and induce catalepsy in rats (8, 9). In the present study verapamil at 5, 10 and 20 mg/kg doses did not inhibit the CAR, neither induced catalepsy nor antagonised apomorphine stereotypy indicating that at these doses verapamil does not have any blocking effect at postsynaptic striatal D 2 and D 1 DA receptors. Our observation that verapamil failed to antagonise apomorphine stereotypy in rats concurs with the finding of Kostowski and Krzascik (10).

Reserpine, by depleting the vesicular stores of DA, and alpha-methyl-p-tyrosine, by inhibiting the synthesis of DA in the nigrostriatal dopaminergic neurons, produce a lack of DA at postsynaptic striatal D 1 & D2 DA receptor sites and induce catalepsy in rats (11). Further, alpha-methyl-p-tyrosine antagonises the SB induced by the DA releaser amphetamine (12). Since verapamil failed to induce catalepsy till 4h testing time interval, and instead of antagonising methamphetamine stereotypy actually potentiated it, it suggests that verapamil, unlike reserpine, does not deplete the intraneuronal vesicular stores of DA, and unlike alpha-methyl-p-tyrosine, does not inhibit the intraneuronal synthesis of DA.

The variety of oral movements or SB induced by high doses of apomorphine occurs as a result of direct stimulation of postsynaptic striatal D 2 DA receptors (8, 12), has a rapid onset and is short-lasting because of rapid apomorphine metabolism (6). Low doses of apomorphine selectively stimulate presynaptically located nigrostriatal D 2 DA autoreceptors and induce long-lasting inhibition of DA synthesis and release (8, 13, 14) and thus produce a lack of DA at postsynaptic striatal D1 and D 2 DA receptors with resultant

catalepsy in rats (7). The low dose apomorphine induced catalepsy has a comparatively delayed onset and is long-lasting (7). Since verapamil at 10 and 20 mg/kg antagonised low dose apomorphine induced catalepsy it indicates that at these doses it blocks the nigrostriatal presynaptic D 2 DA autoreceptors. Our findings agree with that of Argiolas et al (15), that the yawning and penile erection induced by low doses of apomorphine in male rats due to stimulation of the nigrostriatal presynaptic D 2 DA autoreceptors (16), was antagonised by verapamil and corroborate the observation of Tsuda et al (4) that verapamil exerts presynaptic D 2 DA autoreceptor blocking activity.

Methamphetamine induces SB of the oral movement variety by releasing DA from the nigrostriatal dopaminergic neurons with resultant activation of the postsynaptic striatal D 2 DA receptors by the released DA (8, 17). In our study pretreatment with 10 and 20 mg/kg verapamil significantly potentiated methamphetamine stereotypy. However, as pretreatment with verapamil had not potentiated apomorphine stereotypy it suggests that potentiation of methamphetamine stereotypy by verapamil is not due to any facilitatory effect of verapamil at or beyond the postsynaptic striatal D 2 DA receptors. Since neuroleptics, by blocking the presynaptic D 2 DA autoreceptors, increase the intraneuronal synthesis of DA (8, 13), we postulate that verapamil, by blocking the presynaptic D 2 DA autoreceptors, increases the intraneuronal synthesis of DA and hence the intraneuronal stores of DA and makes more DA available for release by methamphetamine with resultant potentiation of methamphetamine stereotypy. Further, its DA neuronal uptake blocking activity (18) might have also contributed to its intensifying effect on methamphetamine stereotypy. Here we would like to emphasize that the calcium channel blocking activity of verapamil does not interfere with its potentiating effect on methamphetamine stereotypy as the release of DA by amphetamines is not calcium-dependent (17).

Verapamil exerted a dose-dependent opposite effect on haloperidol catalepsy. At a lower dose (10 mg/kg) it antagonised, while at a higher dose it potentiated haloperidol catalepsy. We explain our findings on the basis of the observations of other workers as follows. Di Renzo et al (19) have reported a dose-dependent opposite effect of verapamil on the calcium-dependent K^+-evoked release of endogenous DA from tuberoinfundibular neurons incubated *in vitro*. These authors observed that verapamil, at higher doses decreased K^+-evoked DA release by blocking the calcium channels whereas, at lower doses it increased the K^+-evoked release of DA by some other action, probably by its presynaptic D 2 DA autoreceptor blocking activity (4). Further, recent studies have demonstrated that the calcuim channels located on presynaptic axonal terminals and responsible for the release of DA and other neurotransmitters are of the N type and are blocked by omega toxins and are generally insensitive to the L-type calcium channel blockers eg verapamil, dihydropyridines (20). However, in high concentrations, the L-type calcium channel blockers can also

inhibit calcium transport via the N channel and decrease the release of neurotransmitters (20). We hypothesize that the lower dose (10 mg/kg) of verapamil, by blocking the presynaptic D 2 DA autoreceptors, increases the release of DA from the nigrostriatal dopaminergic neurons and thus antagonises haloperidol catalepsy. However, at the higher dose (20 mg/kg) the calcium channel blocking activity of verapamil manifests and prevents the entry of calcium through calcium channels and decreases the release of DA with resultant potentiation of haloperidol catalepsy. Our observation that 20 mg/kg verapamil potentiated haloperidol catalepsy concurs with the observation of Kostowski and Krzascik (10).

To conclude, our study indicates that verapamil dose not block the postsynaptic striatal D 1 and D 2 DA receptors but does block the presynaptic D 2 DA autoreceptors and thereby potentiates methamphetamine stereotypy and at the lower dose (10 mg/kg) antagonises haloperidol catalepsy. Verapamil at the higher dose (20 mg/kg) potentiates haloperidol catalepsy most probably by blocking the calcium channels.

ACKNOWLEDGEMENTS

The generous gift of verapamil hydrochloride from Torrent Laboratories Ltd is gratefully acknowledged.

REFERENCES

1. De Vries DJ, Beart PM, Competitive inhibition of 3_H spiperone binding to D 2 dopamine receptors in striatal homogenates by organic calcium channel antagonists and polyvalent cations. *Eur J Pharmacol* 1985; 106: 133–139.
2. Bagchi SP. Antidopaminergic action of verapamil and several other drugs: inactivation of vesicular dopamine. *Life Sci* 1990; 46: 857–863.
3. Gaggi R, Gianni AM. Effects of calcium antagonists on biogenic amines in discrete brain areas. *Eur J Pharmacol* 1990; 181: 187–197.
4. Tsuda K, Tsuda S, Masuyama Y. Effects of calcium-antagonists on dopamine release in the central nervous system: Possible interactions with D 2–autoreceptors and guanosine triphosphate binding proteins. *Jpn Circ J* 1992; 56: 248–254.
5. Cook L, Weidley EF. Behavioral effects of some psychopharmacological agents. *Ann N Y Acad Sci* 1957; 66: 740–752.
6. Costall B, Naylor RJ. Mesolimbic involvement with behavioural effects indicating antipsychotic activity. *Eur J Pharmacol* 1974; 27: 46–58.
7. Balsara JJ, Bapat TR, Gada VP, Chandorkar AG. Small doses of apomorphine induce catalepsy and antagonize methamphetamine stereotypy in rats. *Psychopharmacology* 1982; 78: 192–194.
8. Seeman P. Brain dopamine receptors. *Pharmacol Rev* 1980; 32: 229–313.
9. Christensen AV, Arnt J, Hyttel J, Larsen JJ, Svendsen O, Pharmacological effects of a specific dopamine D 1 antagonist SCH 23390 in comparison with neuroleptics. *Life Sci* 1984; 34: 1529–1540.
10. Kostowski W, Krzascik P. Effect of certain calcium channel inhibitors on D 2 receptor – mediated responses : Haloperidol – induced catalepsy and apomorphine – induced locomotor changes. *Biog Amines* 1992; 8: 277–287.
11. Hornykiewicz O. Parkinsonism induced by dopaminergic antagonists. In Calne DB, Chase TN, Barbeau A, eds. Dopaminergic mechanisms. New York, Raven Press 1975: 155–164.
12. Wallach MB. Drug induced stereotyped behaviours: Similarities and differences. In Usdin E, ed. Neuropsychopharmacology of monoamines and their

regulatory enzymes. New York, Raven Press 1974: 241–260.

13. Civelli O, Bunzow JR, Grandy DK. Molecular diversity of the dopamine receptors. *Annu Rev Pharmacol Toxicol* 1993; 33: 281–307.

14. Martres MP, Costentin J, Baudry M, Marcais H, Protais P, Schwartz JC. Long-term changes in the sensitivity of pre- and postsynaptic dopamine receptors in mouse striatum evidenced by behavioural amd biochemical studies. *Brain Res* 1977; 136: 319–337.

15. Argiolas A, Melis MR, Gessa GL. Calcium channel inhibitors prevent apomorphine – and oxytocin – induced penile erection and yawning in male rats. *Eur J Pharmacol* 1989; 166: 515–518.

16. Gower AJ, Berendsen HHG, Princen MM, Broekkamp CLE. The Yawning – penile erection syndrome as a model for putative dopamine autoreceptor activity. *Eur J Pharmacol* 1984; 103: 81–89.

17. Seiden LS, Sabol KE, Ricaurte GA. Amphetamine: Effects on catecholamine systems and behaviour. *Annu Rev Pharmacol Toxicol* 1993; 33: 639–677.

18. Mc Gee R, Schneider JE. Inhibition of high affinity synaptosomal uptake systems by verapamil. *Mol Pharmacol* 1979; 16: 877–885.

19. Di Renzo G, Amoroso S, Taglialatela M, Annunziato L. Dual effect of verapamil on K^+–evoked release of endogenous dopamine from arcuate nucleus – median eminence complex. *Neurosci Lett* 1984; 50: 269–272.

20. Pucilowski O. Psychopharmacological properties of calcium channel inhibitors. *Psychopharmacology* 1992; 109: 12–29.