ELSEVIER

European Journal of Pharmacology 412 (2001) 139–144

ejp

www.elsevier.nl/locate/ejphar

Behavioural and anti-psychotic effects of Ca^{2+} channel blockers in rhesus monkey

Gautam Palit *, Auinash Kalsotra [1], Rakesh Kumar [2], Chandishwar Nath, Mangal P. Dubey

Primate Behaviour Laboratory, Division of Pharmacology, Central Drug Research Institute, Post Box 173, Lucknow 226001, India

Received 10 December 1999; received in revised form 17 October 2000; accepted 18 October 2000

Abstract

The potential utility of Ca^{2+} channel blockers in the treatment of various psychiatric disorders has been recently suggested. In the present study, the behavioural and anti-psychotic effects of Ca^{2+} channel blockers were investigated in unrestrained rhesus monkeys (*Macaca mulatta*) living together in a colony. The different behaviours categorised as social, solitary and abnormal were video recorded and analysed. Graded doses of verapamil (5–20 mg/kg, i.m.) and nimodipine (7.5–30 mg/kg, p.o.) produced a mild decrease in social and solitary behaviour without producing any cataleptic posture in the tested monkeys. In order to determine potential antipsychotic effects, Ca^{2+} channel blockers were studied in the model of amphetamine-induced psychosis. Amphetamine, at the dose of 2 mg/kg, i.m., induced suppression of approach, contact, grooming, and feeding, whilst vigilance (checking), stereotyped behaviour and oral hyperkinesia were increased in the monkeys. Pre-treatment with verapamil (10 and 20 mg/kg, i.m.) significantly suppressed amphetamine-induced hypervigilance, stereotypy, oral hyperkinesia and tachypnoea but was unable to reverse other amphetamine-induced behavioural effects. Nimodipine showed insignificant anti-psychotic effects at both 15 and 30 mg/kg doses. These results suggest that verapamil has a definite antipsychotic effect without any extrapyramidal side effects and thus may be of clinical significance in the treatment of psychosis.

Keywords: Ca^{2+} channel blocker; Amphetamine; Behaviour; Antipsychotic; (Rhesus monkey)

1. Introduction

Until a few years ago, Ca^{2+} channel blockers were used mainly for the treatment of cardiovascular diseases, but recently their effects on the central nervous system have started to be elucidated. An increasing body of evidence suggests that they may be beneficial in the treatment of some neurological disorders, such as stroke in acute cerebral ischaemia, migraine, subarachanoid haemorrhage and psychiatric problems, particularly mania (Borrison et al., 1988; Nag et al., 1998; Hollister and Trevino, 1999). Auto radiographic studies have demonstrated that some Ca^{2+} channel blockers cross the blood–brain barrier (McAllen et al., 1984; Puzzle et al., 1989). Moreover, specific recognition sites for Ca^{2+} channel blockers have been identified in the rat cerebral cortex as well as in the human brain (Marangos et al., 1982; Belleman et al., 1983; Peroutka and Allen, 1983). Ca^{2+} channel blockers have been reported to produce behavioural changes in animals (Martin et al., 1996) and to suppress aggressiveness in mice (Srivastava et al., 1997). Ca^{2+} channel blockers have also been shown to be effective against the behavioural effects of NMDA receptor antagonists (Sukhotina et al., 1999). But all these experimental studies have been carried out in rodents, and have concentrated on the behaviour of individual animals rather than the social behaviour of a group. Behaviour is a complex brain function resultant of the relation between an individual and events in the social environment (Sassernath and Chapman, 1976). Amongst

* Corresponding author. Neuropharmacology Unit, Division of Pharmacology, Central Drug Research Institute, Post Box 173, Lucknow 226001, India. Tel.: +91-0522-212411 ext. 4303, 4432; fax: +91-522-223405.

E-mail address: root@cscdri.ren.nic.in (G. Palit).

[1] On practical school training from Birla Institute of Technology and Science, Pilani, India.

[2] Present address: Department of Zoology, Government Post Graduate College, Pithoragarh, UP, India.

0014-2999/01/$ - see front matter
PII: S0014-2999(00)00801-3

the primates, rhesus monkeys (*Macaca mulatta*) have a rich variety of social and individual behaviour, making them interesting subjects for psychopharmacological studies (Vellucci, 1990; Palit et al., 1998). Therefore, it was proposed to study the behavioural and anti-psychotic effects of Ca^{2+} channel blockers in rhesus monkey to obtain results which can be compared more directly with those obtained with human beings. Among the Ca^{2+} channel blockers, verapamil and nimodipine were examined because of their ability to cross the blood–brain-barrier and to interact with specific recognition sites in the brain (Marangos et al., 1982; Borrison et al., 1988).

2. Materials and methods

The subjects for the study were four social colonies of 3–5-year-old adult rhesus monkeys (*M. mulatta*) weighing 4–6 kg. Each colony comprised eight monkeys (one male and seven females). To maintain healthy and disease-free colonies, quarantine was carried out. The colonies were kept in bacterial isolation for 90 days. Thereafter, the monkeys were physically examined and laboratory investigations were carried out. After satisfactory completion of the quarantine period, the colonies were shifted to the experimental room for behavioural studies. The monkeys in the colonies had thus already lived together as a group for some time and were socially adjusted. Pregnant animals were not included in the study. Each colony was housed in a $6.8 \times 4 \times 2.5$-m cage. The normal social and solitary behaviour as well as certain abnormal behavioural patterns were studied. The monkeys were maintained under controlled conditions of temperature, humidity, and air change and under a 12-h light/dark cycle. Food was provided in the morning and evening, and water was available ad libitum by means of an automatic watering system.

To reduce the stress induced by handling and dosing, a single experimenter handled the animals. During that period, monkeys were caught and removed from the cage at least once a week and administered saline intramuscularly or orally.

The animals were observed prior to (baseline control) and after drug or vehicle treatment. A checklist of social, solitary and abnormal behavioural responses based on a modified version (Palit et al., 1997) of the parameters described by Schlemmer and Davis (1983) was used. The behaviour was observed on a video monitor placed in an adjacent room with the help of two strategically placed 180° rotating video cameras, provided with zoom lens, fixed in the behaviour chamber. The behavioural responses were videotaped for analysis and records. The rating was done by an observer unaware of the treatment given.

The following behavioural parameters were monitored in control or treated animals.

2.1. Social behaviour

Social groom: discrete picking or spreading of the hair of a co-inhabitant.
Approach: a monkey walking or running towards another animal from a distant point (0.9 m or more) to within an arm's length distance so that it could touch the other animal.
Huddle: animals sitting together with at least one monkey's arm embracing another animal.
Contact: when the body of one animal is touching the body of another animal but no social action or huddling takes place.
Threat (aggressiveness): eye brows lifted, ear pointed backwards, and mouth open with lower teeth visible, stare and occasional low-pitched vocalization.

2.2. Solitary behaviour

Feeding: manipulation and mastication of food.
Drinking: drinking water from automatic watering system.
Locomotion: the number of ambulations from one point to a distant point (3 ft or more).
Vigilance: the number of observed changes in visual field as indicated by checking response i.e. head and eye movements.
Respiratory rate: respiratory movements per minute in sitting posture.
Resting with eye open: maintaining a relaxed posture, and showing no active behaviour for 30 s or longer while the eyelids remain open for more than 30 s.
Resting with eye closed: maintaining a relaxed posture, and initiating no active behaviour for 30 s or longer while the eyelids were shut for more than 30 s.

2.3. Abnormal behaviour

Stereotyped behaviour (purposeless repetitive movements), oral hyperkinesia (increased movements of mouth) and extrapyramidal signs (tremors, catatonic posture and limb rigidity) were also observed.

All animals of a group were injected with the drug on rotation. On any one day, only one animal from the group was injected with the drug and then its behaviour was observed. A minimum interval of 10 days was maintained between two doses of the drug to the same monkey in order to ensure washout of the previous dose.

Initially, the behaviour of the animal was observed in a drug-or vehicle-free state and this was taken as the normal behaviour. Each monkey was observed in rotation for 1 min every 10 min for 2 h after drug or vehicle treatment i.e. 12 observations for each monkey.

The behavioural responses were scored during the period of observation (1 min) on the basis of their presence (score—1) or absence (score—0), except for locomotion and vigilance behaviour, which were scored by the number of occurrences during the period of observation. In locomotion, each ambulation was given a score of 1 and the total score was noted for each observation. Similarly, in the case of vigilance, each checking was given a score of 1 and the total score was noted for each observation. The scores of a behaviour from the 12 observations were summed up for individual animals and represented the day's score of that behaviour for a monkey. The details of the groups and treatments are given in the tables.

The animal was also observed at 4, 6, 8 and 24 h post treatment for any significant alteration in behaviour.

The significance of the difference between the scores of control and drug-treated groups was determined by Kruskall–Wallis Analysis of Variance (ANOVA) followed by Mann–Whitney test with Bonferoni correction. In the case of respiratory rate, mean ± S.E. value was calculated for each group and Student's t test was applied to calculate the significance of the difference between control and drug-treated groups.

Drugs used were verapamil hydrochloride (Sigma, USA), nimodipine (Cipla Pharmaceuticals, India) and amphetamine sulphate (Sigma). Verapamil and amphetamine were dissolved in 0.9% saline and were administered intramuscularly. Nimodipine was made up in a 1% aqueous suspension of gum acacia and was administered orally.

3. Results

In the present study, the baseline scores observed for each rhesus monkey remained stable within a range of 5–10%, suggesting that the monkeys formed a stable social colony with a normal behavioural profile. There was no difference in behaviour between the vehicle-treated and untreated monkeys.

3.1. Behavioural effect of verapamil

Graded doses of verapamil (5–30 mg/kg, i.m.) per se produced dose-dependent behavioural changes in monkeys. The lower dose of verapamil (5 mg/kg, i.m.) produced insignificant changes in social as well as solitary behaviour.

3.1.1. Social behaviour

Verapamil, at the dose of 10 mg/kg i.m., produced a significant decrease in social grooming, contact, and aggressiveness (threat) but did not affect approach. The higher dose of 20 mg/kg produced a significant decrease in social grooming, approach, contact and aggressive behaviour (Table 1).

3.1.2. Solitary behaviour

At the dose of 10 mg/kg, verapamil did not produce any significant alteration in feeding behaviour. There was a decrease observed in locomotion, vigilance, and self-grooming, while resting with eyes closed was increased. However, when the dose of verapamil was increased to 20 mg/kg, it produced a marked decrease in locomotion, self-grooming and vigilance. There was an increase in resting with eyes open (Table 1). Neither dose of verapamil produced any abnormal behaviour nor extrapyramidal signs-tremors, catatonic posture and limb rigidity.

Behavioural changes were first noted 30 min after drug administration, while the peak effect was observed between 45 and 60 min. The effect lasted for 2–3 h for the 10 mg/kg dose and 3–5 h for the 20 mg/kg dose.

Table 1
Effects of verapamil and nimodipine on social and solitary behavioural responses of rhesus monkey

Behavioural responses	Control	Verapamil (i.m.)		Nimodipine (p.o.)	
		10 mg/kg	20 mg/kg	15 mg/kg	30 mg/kg
Social					
1. Social-grooming	3 (2–4)	1 (1–2)[a]	1 (0–2)[a]	2 (1–2)	1 (0–2)[a]
2. Approach	2 (0–3)	2 (1–3)	1 (0–1)[a]	1 (0–1)[a]	1 (0–1)[a]
3. Contact	2 (1–4)	1 (0–2)[a]	1 (0–1)[a]	2 (0–2)	1 (0–1)[a]
4. Aggressiveness	2 (1–3)	1 (0–1)[a]	1 (0–1)[a]	2 (1–3)	1 (0–1)[a]
Solitary					
1. Locomotion	8 (7–10)	6 (5–7)	5 (4–6)[b]	5 (5–7)[a]	5 (3–7)[a]
2. Vigilance	10 (8–12)	6 (6–8)[a]	5 (5–7)[b]	6 (5–8)[a]	6 (4–7)[b]
3. Feeding	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–2)	1 (0–1)
4. Self-grooming	4 (2–5)	2 (2–3)[a]	2 (0–3)[a]	4 (3–4)	3 (2–4)
5. Resting with eyes open	5 (4–7)	7 (6–8)[a]	8 (7–9)[a]	6 (5–7)	7 (6–8)[a]

Behavioural responses are expressed as median scores with range (lowest–highest) of scores in parentheses.
[a] $P < 0.05$, significant difference from control.
[b] $P < 0.01$, significant difference from control.

3.2. Behavioural effect of nimodipine

Graded doses of nimodipine (7.5–30 mg/kg, p.o.) per se altered the normal social and solitary behaviour of monkeys. The lower dose of nimodipine (7.5 mg/kg p.o.) produced insignificant changes in social as well as solitary behaviour.

3.2.1. Social behaviour

Nimodipine at the dose of 15 mg/kg produced a significant decrease in approach whereas no changes were observed in social grooming, contact and aggressiveness. When the dose of nimodipine was increased to 30 mg/kg, it produced a significant decrease in grooming, approach, contact and aggressiveness (Table 1).

3.2.2. Solitary behaviour

Nimodipine 15 mg/kg caused no significant change in feeding but a decrease in locomotion and vigilance was observed. Self-grooming and resting with eyes open were not affected. The higher dose of 30 mg/kg produced a significant decrease in locomotion, vigilance and feeding while resting with eyes open was increased (Table 1). There was no abnormal behaviour or extrapyramidal signs-tremors, catatonic posture and limb rigidity were not seen after the administration of the two doses of nimodipine.

The onset of action occurred 30 min after drug administration with peak effects appearing at 45–60 min. Duration of action was 2–3 h for the 15-mg/kg and 35 h for the 30-mg/kg doses of nimodipine.

3.3. Behavioural effects of amphetamine

3.3.1. Social behaviour

Amphetamine (2 mg/kg, i.m.) significantly suppressed social grooming, approach and contact (Table 2).

3.3.2. Solitary behaviour

Amphetamine also induced a complete suppression of food intake and grooming, and significantly increased the respiratory rate (52 ± 1.42 as compared to control—39.2 ± 1.02). Further, the monkeys were hypervigilant i.e. there was marked increase in head and eye movements. The treated animals repeatedly looked around the cage in a random fashion and the duration of checking lasted for 30–45 min. Later, amphetamine induced a stereotypic behaviour (repetitive movements of forearms) and oral hyperkinesia (Table 2).

The onset of action was 30 min after drug treatment, the peak effect was observed after 45–60 min and the effect lasted for 6 h.

3.4. Effect of pretreatment with verapamil and nimodipine on amphetamine-induced behavioural effects

Amphetamine (2 mg/kg)-induced hypervigilance, stereotypy and oral hyperkinesia were significantly suppressed by pre-treatment (30 min prior to amphetamine) with verapamil 20 mg/kg, i.m. without affecting the amphetamine-induced suppression of grooming, approach, contact and feeding. Verapamil significantly decreased the tachypnoea induced by amphetamine. Pre-treatment with nimodipine (30 mg/kg, p.o.) 45 min prior to amphetamine

Table 2
Effects of pre-treatment with verapamil (20 mg/kg, i.m.) and nimodipine (30 mg/kg, p.o.) on amphetamine (2 mg/kg, i.m.)-induced behavioural changes in rhesus monkeys

Behavioural responses	Control	Amphetamine	Verapamil + Amphetamine	Nimodipine + Amphetamine
Social				
1. Approach	2 (1–3)	0 (0–2)[a]	0 (0–1)	0 (0–1)
2. Contact	2 (0–3)	0 (0–1)[a]	0 (0–1)	0 (0–2)
3. Grooming	3 (2–4)	0 (0–1)	0 (0–2)	0 (0–1)
Solitary				
1. Feeding	2 (1–3)	0 (0–1)[a]	0 (0–2)	0 (0–1)
2. Grooming	2 (1–3)	0 (0–1)[a]	0 (0–1)	0 (0–2)
3. Vigilance	10 (8–12)	35 (30–37)[a]	12 (9–14)[b]	29 (27–31)
4. Respiratory rate	39.2 ± 1.02	52.9 ± 1.14[a]	41 ± 1.2[b]	41 ± 1.5[b]
Abnormal				
1. Stereotypy +	0 (0–0)	3 (2–3)[a]	0 (0–1)[b]	2 (1–2)
2. Oral hyperkinesia +	0 (0–0)	2 (1–2)[a]	0 (0–0)[b]	2 (1–2)

Behavioural responses are expressed as median scores with range (lowest–highest) of scores in parentheses; respiratory rate is shown as mean ± S.E.
+ Score = Frequency of occurrence per minute: 1 = 1–3, 2 = 4–6, 3 = 7–12, 4 ≥ 12.
[a] Significant difference ($P < 0.05$–0.01) from control.
[b] Significant difference ($P < 0.05$–0.01) from Amphetamine.

did not reverse the amphetamine-induced behavioural changes significantly but did diminish the increase in respiratory rate (Table 2).

4. Discussion

Rhesus monkeys live in organised social groups and exhibit a range of behaviours involving other members of the colony (Vellucci, 1990; Schlemmer and Davis, 1983). Evidence of drug-induced behavioural alterations may be more predictive of effects in humans than when it is obtained from socially isolated animals removed from a familiar environment and restrained artificially (Palit et al., 1998; Schlemmer and Davis, 1983). Therefore, in the present study, the effects of Ca^{2+} channel blockers were investigated on behavioural responses in rhesus monkeys living together in a social colony.

Verapamil and nimodipine both caused a dose-dependent decrease in social and solitary behaviour without inducing any abnormal behaviour. The anti-aggressive effect of nimodipine has also been reported in mice by other workers (Hoffmeister et al., 1982; Pucilowski, 1992). The inhibitory effects of verapamil on locomotion and aggressiveness have also been documented in rodent studies (Pant et al., 1995; Martin et al., 1996; Srivastava et al., 1997).

Furthermore, verapamil but not nimodipine was found to antagonise amphetamine-induced changes in behaviour, which may indicate that it has anti-psychotic potential. Amphetamine abuse by humans may lead to a psychotic state closely resembling paranoid schizophrenia (Janwoski and Risch, 1979) and amphetamine has been widely studied for its behavioural changes linked with hyperdopaminergic activity and the dopamine theory of schizophrenia (Palit, 1995). Amphetamine-induced hyperactivity in rodents exhibits a high degree of pharmacological isomorphism, a form of predictive validity, and can be used as a model to test the efficacy of clinical treatment of schizophrenia (Geyer and Markou, 1995).

In primates, amphetamine-induced stereotypy, tachypnoea, hypervigilance and oral hyperkinesia appear to be similar to the positive symptoms of schizophrenia while marked social withdrawal i.e. suppression of approach, contact and social grooming, resembles the negative symptoms (Palit, 1995). Verapamil decreased the tachypnoea and hypervigilance and completely blocked the stereotypy and oral hyperkinesia produced by amphetamine, but was unable to reverse the social withdrawal. These findings suggest that verapamil can attenuate only the positive symptoms of psychosis. Other Ca^{2+} channel blockers like nifedipine and flunarizine have also been reported to block amphetamine-induced hyperactivity in mice (Grebb, 1986, Pucilowski et al., 1995).

Amphetamine is an established releaser of the catecholamines norepinephrine and dopamine. Norepinephrine is mainly involved in locomotor changes whereas dopamine has been implicated in the stereotypy and hyperlocomotor activity seen with amphetamine (Hoffman and Lefkowitz, 1996). Therefore, inhibition of amphetamine-induced effects by verapamil may be the result of a decrease in either the release of norepinephrine and dopamine or the activity of adrenoceptors and dopamine receptors. There are reports that verapamil inhibits the release and synthesis of catecholamines, thereby decreasing their synaptic concentration (Uretksy et al., 1979; Stark et al., 1984). Moreover, verapamil also exerts an antagonistic effect against α-adrenoceptor (Atlas and Adler, 1981) and dopamine receptors (Borrison et al., 1988). Thus, the inhibitory influence of verapamil on the amphetamine-induced effects may be due to a decrease in the release of catecholamines and blockade of dopamine receptors and α-adrenoceptors. The most noteworthy point here is that verapamil, unlike classical antipsychotics, does not produce any extra pyramidal side effects. It seems that the inhibitory influence of verapamil on dopamine activity is more prominent in limbic areas than in the nigrostriatal system.

Nimodipine did not exhibit any marked reversal of amphetamine-induced behavioural changes in rhesus monkeys. The success of verapamil and failure of nimodipine, a dihydropyridine, against amphetamine-induced behavioural changes might be attributed to the fact that the anti-adrenergic effects of Ca^{2+} channel blockers of the dihydropyridine group are much weaker than those of verapamil (Larsson et al., 1984; Godfraind et al., 1986). However, the possibility that verapamil interfered with the entry of amphetamine into the brain, due to inhibition of a *p*-glycoprotein transport mechanism in blood–brain-barrier system, may be another contributory factor in reversing amphetamine-induced behavioural changes.

In conclusion, the data from the present study indicate that Ca^{2+} channel blockers have a definite role in the regulation of behavioural responses. Both verapamil and nimodipine caused a dose-dependent decrease in social and solitary behaviour. Verapamil further had an antipsychotic-like action without producing any extra pyramidal symptoms. Thus, these drugs have potential clinical utility in the management of psychiatric disorders.

Acknowledgements

The authors are grateful to Dr. S.K. Mandal, Head, Division of Biometry, Central Drug Research Institute, Lucknow, for his assistance in statistical analysis of the data.

References

Atlas, D., Adler, M., 1981. α-Adrenergic antagonists as possible Ca^{2+} channel inhibitors. Proc. Natl. Acad. Sci. U. S. A. 78, 1237–1243.

Belleman, P., Stead, A., Towart, R., 1983. Dihydropyridine receptors in rat brain labelled with (^{3}H) nimodipine. Proc. Natl. Acad. Sci. U. S. A. 80, 2356–2360.

Borrison, R.L., Mclaren, M.C., Demartines, N., Diamond, B., 1988. Ca^{2+} channel antagonists: interaction with dopamine, schizophrenia and tardive dyskinesia. In: Wolf, M.E., Mosnaim, A.D. (Eds.), Tardive Dyskinesia: Biological Mechanisms and Clinical Aspects. American Psychiatric Press, Washington, DC, pp. 217–223.

Geyer, M.A., Markou, A., 1995. Animal models of psychiatric disorders. In: Bloom, F.E., Kupfer, D.J. (Eds.), Psychopharmacology: The Fourth Generation of Progress. Raven Press, New York, pp. 787–798.

Godfraind, T., Miller, R., Wibo, M., 1986. Ca^{2+} antagonism and calcium entry blockade. Pharmacol. Rev. 38, 321–416.

Grebb, J.A., 1986. Nifedipine and flunarizine block amphetamine induced behavioural stimulation in mice. Life. Sci. 38, 2375–2381.

Hoffman, B.B., Lefkowitz, R.J., 1996. Catecholamines, sympathomimetic drugs, and adrenoceptor antagonists. In: Hardman, J.G., Limbird, L.E., Molinoff, P.B., Rudden, R.W., Gillman, A.G. (Eds.), Goodman and Gillman's The Pharmacological Basis of Therapeutics. McGraw-Hill, New York, pp. 199–248.

Hoffmeister, F., Benz, U., Heise, A., Krause, P.H., Neuser, U., 1982. Behavioural effects of nimodipine in animals. Drug Res. 32 (1), 347–360.

Hollister, L.E., Trevino, E.S., 1999. Ca^{2+} channel blockers in psychiatric disorders. Can. J. Psychiatry 44, 658–664.

Janwoski, D.S., Risch, C., 1979. Amphetamine psychosis and psychotic symptom. Psychopharmacology 65, 73–77.

Larsson, B., Hogestat, E.D., Mattiasson, A., Andersson, K.E., 1984. Differential effects of nifedipine, verapamil and diltiazem on noradrenaline induced contraction, adrenergic transmitter release, and alpha-adrenoceptor binding in female rabbit urethra. Naunyn-Schmiedeberg's Arch. Pharmacol. 326, 14–21.

Marangos, P.J., Patel, J., Miller, C., Martino, A.M., 1982. Specific Ca^{2+} antagonists binding sites in brain. Life Sci. 31, 1575–1580.

Martin, M.I., Delval, V.L, Colado, M.I., Goicoechea, C., Alfaro, M.J., 1996. Behavioral and analgesic effects induced by administration of nifedine and nimodipine. Pharmacol. Biochem. Behav. 55, 93–98.

McAllen, T.A., Nath, R.O., Thievem, K., 1984. The effects of a Ca^{2+} antagonist (nimodipine) on basal cerebral blood flow and reactivity to various agonists. Stroke 15, 527–530.

Nag, D., Garg, R.K., Verma, M.A., 1998. Randomised blind controlled study of nimodipine in acute cerebral ischaemic stroke. Ind. J. Physiol. Pharmacol. 42, 555–558.

Palit, G., 1995. Quantitative assessment of amphetamine induced behavioural changes in rhesus monkeys *Macaca mulatta*. Ind. J. Expt. Biol. 33, 980–982.

Palit, G., Kumar, R., Gupta, M.B., Saxena, R.C., Patnaik, G.K., Dhawan, B.N., 1997. Quantification of behaviour in social colonies of rhesus monkey. Ind. J. Physiol. Pharmacol. 41, 219–226.

Palit, G., Kumar, R., Chowdhary, S.R., Gupta, M.B., Saxena, R.C., Srimal, R.C., Dhawan, B.N., 1998. A primate model of anxiety. Eur. Neuropsychopharmacol. 8, 195–201.

Pant, K.K., Mukerjee, D., Nath, C., 1995. Some behavioural effects of verapamil and nifedipine in mice. Ann. Neurosci. 5, 46–51.

Peroutka, S.J., Allen, G.S., 1983. Ca^{2+} channel antagonist binding sites labelled by (^{3}H) Nimodipine in human brain. J. Neurosurg. 59, 933–937.

Pucilowski, O., 1992. Psychopharmacological properties of Ca^{2+} channel inhibitors. Psychopharmacology 109, 12–29.

Pucilowski, O., Plaznik, A., Overstreet, D.H., 1995. Isradipine suppresses amphetamine induced conditioned place preference and locomotor stimulation in the rat. Neuropsychopharmacology 12, 239–244.

Puzzle, C., DiPier, V., Pantene, P., Raiser, M., Lens, G.L., 1989. Influence of nimodipine on cerebral blood flow in human ischaemia. J. Neurol. 236, 199–202.

Sassernath, E.N., Chapman, L.F., 1976. Primate social behaviour as a method of analysis of drug action. Studies with THC in monkey. Fed. Proc. 35, 2238–2244.

Schlemmer, R.F., Davis, J.M., 1983. A comparison of three psychomimetic induced models of psychosis in non-human primate social colonies. In: Miczek, K.A. (Ed.), Ethnopharmacology: Primate Models of Neuropsychiatric Disorders. Alanliss, New York, pp. 33–78.

Srivastava, S.K., Nath, C., Sinha, J.N., 1997. Evidence for antiaggressive property of some Ca^{2+} channel blockers. Pharmacol. Res. 35, 435–438.

Stark, K., Spath, L., Wickmam, T., 1984. Effect of verapamil, diltiazem and rysoidine on the release of dopamine and acetylcholine in rabbits caudate nucleus slices. Naunyn-Schmiedeberg's Arch. Pharmacol. 325, 124–130.

Sukhotina, I.A., Dravolina, O.A., Medvedev, I.O., Bespalov, A.J., 1999. Effect of Ca^{2+} channel blockers on behaviours induced by the *N*-methyl-*D*-aspartate receptor antagonist, dizocilpine, in rats. Pharmacol. Biochem. Behav. 63, 569–580.

Uretksy, N.J., Kamal, L., Snodgrass, S.R., 1979. Effect of divalent cations on the amphetamine induced stimulation of [^{3}H] catechol synthesis in the striatum. J. Neurochem. 32, 1951–1960.

Vellucci, S.A., 1990. Primate social behaviour—anxiety or depression. Pharmacol. Ther. 47, 167–180.