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Effects of Ca^{2+} channel blockers on apomorphine, bromocriptine and morphine-induced locomotor activity in mice

Ahmet Doğrul *, Özgür Yeşilyurt

Department of Pharmacology, Faculty of Medicine, Gülhane Medical Military Academy, 06018 Etlik, Ankara, Turkey

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Abstract

The effects of L-type voltage-dependent Ca^{2+} channel blockers on apomorphine, bromocriptine and morphine-induced changes in locomotor activity were examined in mice. Apomorphine (4 mg/kg) and morphine (20 mg/kg) produced locomotor stimulation. Bromocriptine (8 mg/kg) produced a biphasic effect on motor behaviour, an early depressant phase, followed by locomotor stimulation. Amlodipine (2.5 mg/kg), nicardipine (10 mg/kg), diltiazem (10 mg/kg) and verapamil (10 mg/kg), which by itself did not affect locomotor activity, inhibited the stimulant phase of bromocriptine without altering the depressant phase, while they did not affect apomorphine- and morphine-induced locomotor stimulation. Apomorphine, bromocriptine and morphine-induced locomotor stimulation was decreased by SCH 23390 (*R*-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepine-7-ol) (0.05 mg/kg) or haloperidol (0.1 mg/kg). These results indicate that L-type voltage-dependent Ca^{2+} channels are involved in the motor stimulant effect of bromocriptine, but not in apomorphine- and morphine-induced locomotor stimulation. The effects of Ca^{2+} channel blockers on the dopaminergic system appears not to be directly related to dopamine receptor blockade.

Keywords: Ca^{2+} channel blocker; Locomotor activity; Dopamine

1. Introduction

Ca^{2+} channel blockers are used in the treatment of certain cardiovascular and neurological disorders and occasionally induce side-effects such as Parkinsonism and movement disorders. Some studies have provided evidence that, in the central nervous system, Ca^{2+} channel blockers directly affect certain neuronal functions which are known to be Ca^{2+}-dependent, such as neurotransmitter release and synthesis, and neuronal excitability (Miller, 1987). Radioligand binding studies have shown that some Ca^{2+} channel blockers interact with dopamine receptors (Cronin, 1982; De Vries and Beart, 1985; Casellas et al., 1990), mainly causing suppression of dopaminergic neurotransmission. Several Ca^{2+} channel blockers have been found to antagonize or suppress physiological and behavioral responses elicited by direct and indirect dopaminergic agonists (Pucilowski, 1992). The involvement of L-type Ca^{2+} channels in dopamine release is controversial. There are reports that Ca^{2+} channel blockers have no effect on dopamine release (Gaggi et al., 1993), whereas others have shown that Ca^{2+} channel blockers decrease (Starke et al., 1984; Kato et al., 1992; Mena et al., 1995), or even increase (Nordström et al., 1986; Tsuda et al., 1992) dopamine release. Interestingly, some Ca^{2+} channel blockers have been found to be effective to block dopaminergic responses from sensitized receptors, due to repeated electroconvulsive shock (Antkiewicz-Michaluk et al., 1994a,b), morphine abstinence (Antkiewicz-Michaluk et al., 1990, 1993, 1994a) or neuroleptic withdrawal (Grebb et al., 1987; Mamczarz et al., 1994). Although much evidence appears to favor the notion that Ca^{2+} channel blockers have antidopaminergic properties, some discrepancies and inconsistencies in the literature preclude total acceptance of this hypothesis (Pucilowski, 1992).

Dopamine is one of the major neurotransmitters involved in locomotion. Measurement of spontaneous locomotor activity has been used to obtain preliminary information on the behavioral properties of drugs acting on dopaminergic system. The dopamine receptor agonists, apomorphine (mixed dopamine D_1/D_2 receptor agonist)

* Corresponding author. Tel: +90-312-3044767/1692; Fax: +90-312-3234923; E-mail: adogrul@obs.gata.edu.tr

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Table 1
Effects of amlodipine (2.5 mg/kg), nicardipine (10 mg/kg), diltiazem (10 mg/kg) and verapamil (10 mg/kg) on spontaneous locomotor activity in mice

Challenge (mg/kg)	Total counts ± S.E.M.
Saline	19607 ± 2906
Amlodipine (2.5)	18620 ± 3316
Nicardipine (10)	15463 ± 2544
Diltiazem (10)	16838 ± 1702
Verapamil (10)	15996 ± 1829

The results shown are mean total counts ± S.E.M. for eight animals, obtained cumulatively for 2 h after treatment. The data were analyzed by one-factor analysis of variance. No significant differences between groups were observed ($F(4,35) = 1.27$, $P = 0.29$).

and bromocriptine (dopamine D_2 receptor agonist), produce dose-dependent locomotion in mice. However, while bromocriptine shares many properties with other dopamine D_2 receptor agonists, it has a number of unusual properties. Bromocriptine cannot be considered a directly acting agonist like apomorphine, since reserpine and α-methyl-*p*-tyrosine inhibit the locomotor stimulant effects of bromocriptine (Johnson et al., 1976). It has been hypothesized that bromocriptine sensitizes dopamine D_2 receptors to other agonists and/or requires concomitant dopamine D_1 receptor stimulation which is usually provided by endogenous dopamine for many of its behavioral effects to be manifested (Jackson and Jenkins, 1985). Morphine and related opioids can stimulate motor activity (Oliverio and Castellano, 1974), an effect hypothesized to depend on brain dopamine levels (Carroll and Sharp, 1972; Longoni et al., 1987), but alternative mechanisms have also been proposed (Ayhan and Randrup, 1973; Oka and Hosoya, 1976; Vaccarino et al., 1986; Jacquet et al., 1987; Sansone et al., 1987). There have been some discrepancies and inconsistencies in the literature regarding Ca^{2+} channel blockers that interact with the action of stimulants by increasing dopaminergic function. However, strain differences may play a role in the effectiveness of dopaminergic drugs (Cabib and Puglisi-Allegra, 1988; Shannon et al., 1991; Skrinskaya et al., 1992), so generalization of results from various mouse strains are difficult.

In order to examine the functional significance of the interaction between L-type voltage-dependent Ca^{2+} channels and central dopaminergic mechanisms, we studied the effects of L-type voltage-dependent Ca^{2+} channel blockers, amlodipine, nicardipine, diltiazem and verapamil, on apomorphine, bromocriptine and morphine-induced locomotion, where dopamine and dopamine release or its modulation are thought to play a major role in controlling locomotor activity.

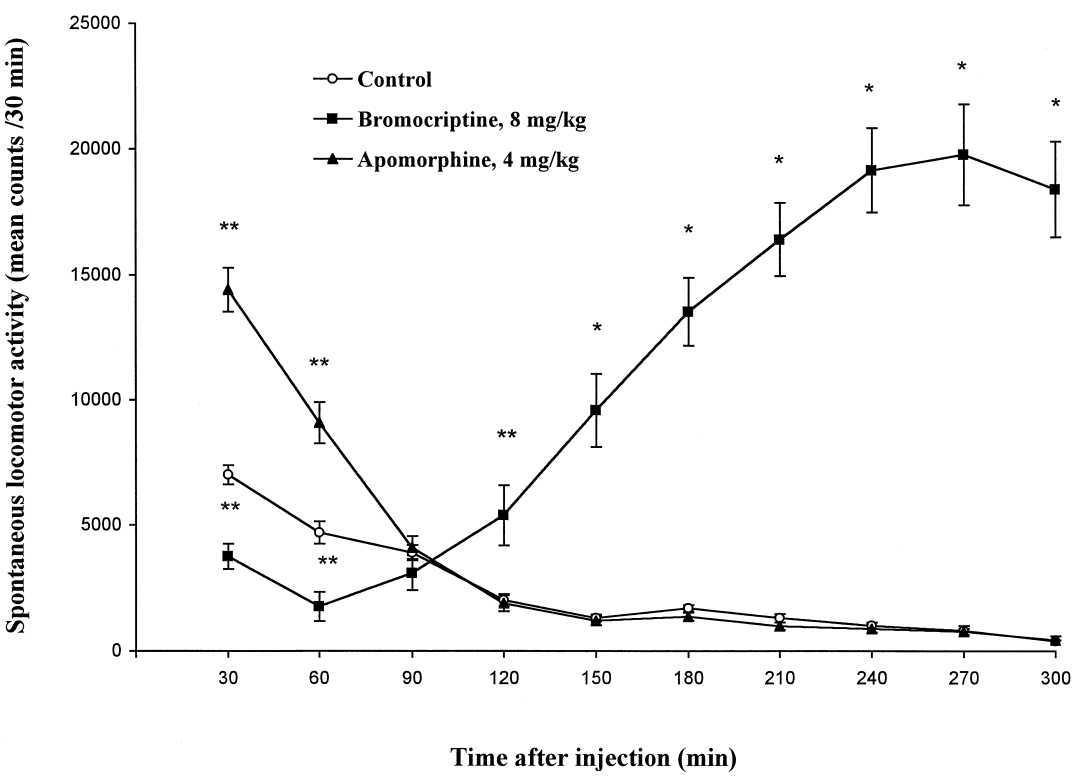

Fig. 1. Time course of changes in spontaneous locomotor activity of mice injected with apomorphine (4 mg/kg), bromocriptine (8 mg/kg) or vehicle (saline and 0.05% tartaric acid). Each point represents the mean spontaneous locomotor activity counts ± S.E.M. from eight animals for 30 min. The data were analyzed by two-way repeated measures analysis of variance and post hoc comparisons were undertaken with the Scheffé test. Apomorphine and bromocriptine had a significant effect on total locomotor activity ($F(2,210) = 91.9$, $P < 0.01$), while a significant treatment and time interaction was seen ($F(18,210) = 16.7$, $P < 0.01$). Statistically significant differences from vehicle: $^{**}P < 0.05$, $^{*}P < 0.01$.

2. Materials and methods

2.1. Animals

Adult female Swiss–Webster mice (25–30 g) were used. They were placed in a quiet, temperature- and humidity-controlled room (22 ± 3°C and 60 ± 5%, respectively) in which a 12/12-h light–dark cycle was maintained (0800–2000 h light). Free access to food and water was allowed, except during experimentation.

2.2. Locomotor activity measurement

Immediately following the appropriate drug treatment, spontaneous locomotor activity of each mouse was measured with a photocell motility meter (Opto Varimex Minor, Columbus, USA). Spontaneous locomotor activity was monitored for 5 h for bromocriptine and 2 h, for apomorphine and morphine. In experiments in which the effects of bromocriptine and apomorphine were investigated, spontaneous locomotor activity was monitored for 5 h in view of bromocriptine's biphasic effect on locomotion (Jackson et al., 1990) and the effect of morphine was monitored for 2 h. The number of crossings of the infrared beam by each mouse was recorded every 30 min. The animals had not been handled previously and were not habituated to the activity cage before the experiments. Each animal was used only once and the animals were killed immediately after termination of the recording period.

Ca^{2+} channel blockers, SCH 23390 and haloperidol were injected 15 min before apomorphine, bromocriptine or morphine administration. Each experimental group was made up of eight animals.

2.3. Drugs

The drugs used were: amlodipine besylate (Pfizer, Turkey), nicardipine hydrochloride (Sandoz, Turkey), apomorphine, diltiazem and verapamil hydrochloride (Sigma, USA), bromocriptine mesylate and morphine hydrochloride (Sandoz, Switzerland), SCH 23390 maleate (*R*-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepine-7-ol; Schering, USA) and haloperidol (Research Biochemical International, USA). All the drugs were freshly prepared by dissolving them in saline, except for bromocriptine which was dissolved in 0.05% tartaric

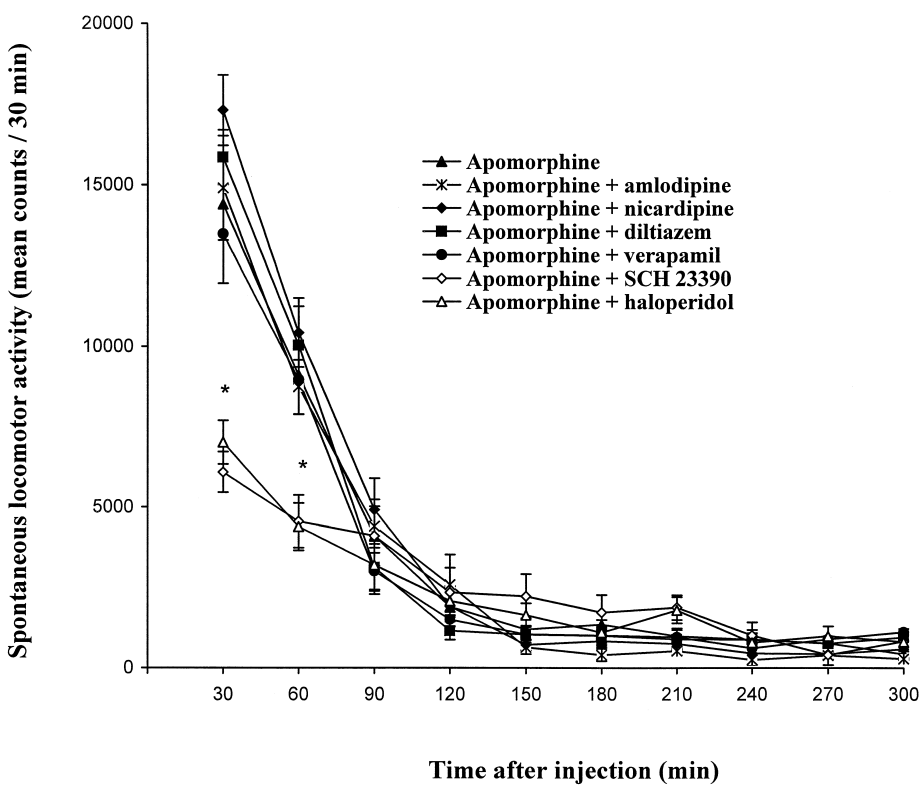

Fig. 2. The effects of amlodipine (2.5 mg/kg), nicardipine (10 mg/kg), diltiazem (10 mg/kg), verapamil (10 mg/kg), SCH 23390 (0.05 mg/kg) and haloperidol (0.1 mg/kg) pretreatment on apomorphine-induced (4 mg/kg) locomotor stimulation in mice. Each point represents the mean spontaneous locomotor activity counts ± S.E.M. from eight animals for 30 min. The data were analyzed by two-way repeated measures analysis of variance and post hoc comparisons were undertaken with the Scheffé test. There is a significant difference between the effects of SCH 23390 and those of haloperidol on apomorphine-induced locomotion and a significant interaction between treatment and time, respectively ($F(6,490) = 12.89$, $P < 0.01$ and $F(54,490) = 6.77$, $P < 0.01$). Statistically significant differences from apomorphine alone for SCH 23390 and haloperidol: $^{*}P < 0.01$.

acid and haloperidol, which was dissolved in a minimum volume of glacial acetic acid and diluted with water. All the drugs were administered in a volume of 5 ml/kg i.p. Appropriate vehicles were used in all experiments.

2.4. Statistical analyses

Result are presented as mean number of counts ± S.E.M. Behavioral data were analysed by the appropriate analysis of variance, followed by post hoc Scheffé test.

3. Results

3.1. Effects of Ca^{2+} channel blockers on locomotor activity in control mice

Amlodipine (2.5 mg/kg), nicardipine (10 mg/kg), diltiazem (10 mg/kg) and verapamil (10 mg/kg), did not significantly alter spontaneous locomotor activity over a 2-h observation period ($F(4,35) = 1.27$, $P = 0.29$). The mean total locomotor activity of the control group and of Ca^{2+} channel blocker-injected animals is given in Table 1.

3.2. Effects of Ca^{2+} channel blockers or dopamine receptor antagonists on apomorphine and bromocriptine-induced locomotor activity

Control animals which were given either saline or vehicle (tartaric acid) displayed a gradual reduction in spontaneous locomotor activity in 120 min and this reduced activity continued for the 5 h of observation. Apomorphine (4 mg/kg) produced initial locomotor stimulation. Spontaneous locomotor activity counts at 30 min and 1 h after drug administration were significantly (both $P < 0.05$) higher when compared with controls. At 90 min after apomorphine injection, the spontaneous locomotor activity counts of these animals were similar to that of the control mice (Fig. 1). Consistent with previous findings (Jackson et al., 1988, 1990, 1995), bromocriptine (8 mg/kg) exerted a biphasic effect on spontaneous locomotor activity in mice. Fig. 1 shows the time course of changes in spontaneous locomotor activity after bromocriptine administration. Bromocriptine produced an immediate and significant locomotor depression 30 and 60 min after injection (both $P < 0.05$) which was about 50% of that of the vehicle control. This effect was later changed into locomo-

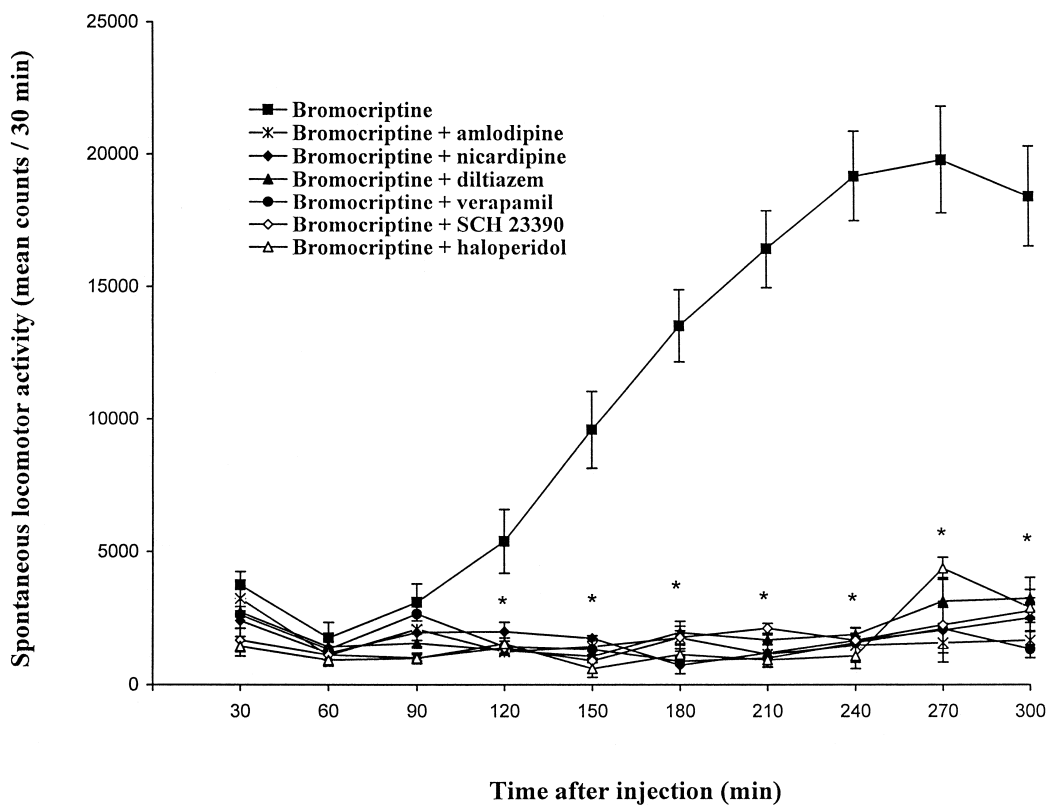

Fig. 3. The effects of amlodipine (2.5 mg/kg), nicardipine (10 mg/kg), diltiazem (10 mg/kg), verapamil (10 mg/kg), SCH 23390 (0.05 mg/kg) and haloperidol (0.1 mg/kg) pretreatment on bromocriptine-induced (8 mg/kg) locomotion. Each point represents the mean spontaneous locomotor activity counts ± S.E.M. from eight animals for 30 min. The data were analysed by two-way repeated measures analysis of variance and post hoc comparisons were undertaken with the Scheffé test. There is a significant difference between the effects of Ca^{2+} channel blockers, SCH 23390 and those of haloperidol treatment on bromocriptine-induced locomotion and a significant interaction between treatment and time, respectively ($F(6,490) = 122.40$, $P < 0.01$ and $F(54,490) = 7.15$, $P < 0.01$). * Statistically significant differences from bromocriptine alone for each Ca^{2+} channel blocker, SCH 23390 and haloperidol: * $P < 0.01$.

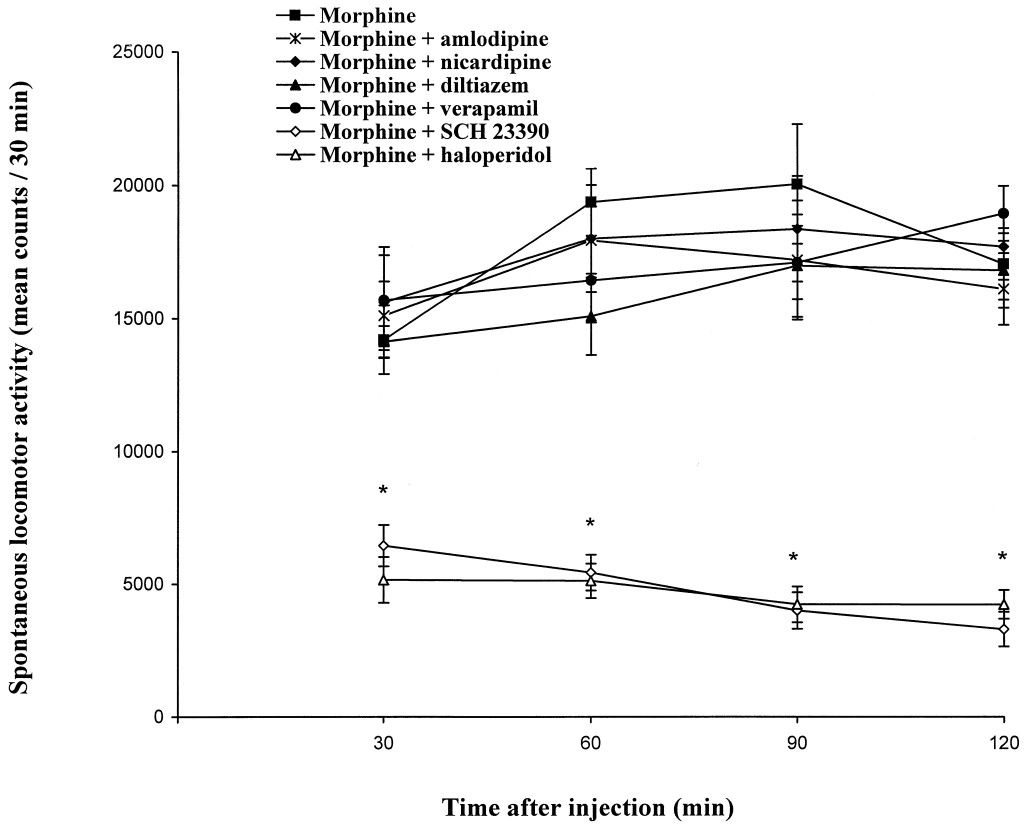

Fig. 4. The effects of amlodipine (2.5 mg/kg), nicardipine (10 mg/kg), diltiazem (10 mg/kg), verapamil (10 mg/kg)), SCH 23390 (0.05 mg/kg) or haloperidol (0.1 mg/kg) pretreatment on morphine-induced (20 mg/kg) locomotor stimulation in mice. The data were analysed by two-way repeated measures analysis of variance and post hoc comparisons were undertaken with the Scheffé test. There is a significant difference between the effects of SCH 23390 and haloperidol treatments on morphine-induced locomotion ($F(6,196) = 79.29$, $P < 0.01$). There is no significant interaction between treatment and time ($F(18,196) = 1.01$, $P = 0.45$). * Statistically significant differences from morphine alone for SCH 23390 and haloperidol: $^{*}P < 0.01$.

tor stimulation which continued for 5 h. As shown in Fig. 2, amlodipine (2.5 mg/kg), nicardipine (10 mg/kg), diltiazem (10 mg/kg) and verapamil (10 mg/kg) pretreatment did not affect the apomorphine-induced alteration of locomotor activity. Ca^{2+} channel blockers did not affect the bromocriptine-induced locomotor depression at 30 and 60 min after bromocriptine injection, however all the Ca^{2+} channel blockers inhibited locomotor stimulation between 2–5 h (Fig. 3). SCH 23390 (0.05 mg/kg) or haloperidol (0.1 mg/kg) decreased apomorphine-induced locomotor stimulation (Fig. 2). The stimulant effect of bromocriptine was abolished by SCH 23390 (0.05 mg/kg) or haloperidol (0.1 mg/kg) without alteration of the bromocriptine-induced depressant phase (Fig. 3). SCH 23390 or haloperidol alone exerted no significant effect on spontaneous locomotor activity (data not shown).

3.3. Effects of Ca^{2+} channel blockers or dopamine receptor antagonists on morphine-induced locomotor activity

Morphine (20 mg/kg) produced a consistent and marked increase in spontaneous locomotor activity in saline-pretreated mice, characterized by continuous circling of the perimeter of the cage (a running fit). This excitation became apparent within 30 min and persisted for 2 h after morphine administration. None of the Ca^{2+} channel blockers used affected morphine-induced increase in locomotor activity, but SCH 23390 (0.05 mg/kg) or haloperidol (0.1 mg/kg) inhibited the activity-increasing effects of morphine (Fig. 4).

4. Discussion

The present results demonstrated that L-type voltage-dependent Ca^{2+} channel blockers prevent the locomotor stimulation induced by bromocriptine, but do not alter the locomotor stimulation induced by apomorphine or morphine. Our findings indicate that dopaminergic receptors are involved in apomorphine-, bromocriptine- and morphine-induced locomotion, since the dopamine D_1 receptor antagonist, SCH 23390, or dopamine D_2 receptor antagonist, haloperidol, inhibited this stimulant-induced locomotion, in line with results of previous studies (Longoni et al., 1987; Zarrindast and Zarghi, 1992; Magnus-Ellenbroek and Havemann-Reinecke, 1993).

It is generally accepted that the excitatory action of apomorphine on locomotion is due to activation of post-synaptic dopamine receptors (Kelly et al., 1975).

Bromocriptine, like other dopamine D_2 receptor agonists, produces a biphasic effect in mice (Fuxe et al., 1978; Jenkins and Jackson, 1985): an early locomotor depression followed by excitation, probably due to stimulation of presynaptic and postsynaptic dopamine D_2 receptors, respectively (Jackson et al., 1990, 1995). It has been shown that bromocriptine-induced locomotor stimulation is blocked by reserpine and α-methyl-*p*-tyrosine pretreatment (Di Chiara et al., 1977; Jenkins and Jackson, 1985), so the behavioral excitation induced by bromocriptine is crucially dependent on concomitant D_1 receptor stimulation which is usually provided by endogenous dopamine (Jackson and Hashizume, 1987; Jackson et al., 1988; Zarrindast and Eliassi, 1991). However, the depressant phase is unaffected by α-methyl-*p*-tyrosine pretreatment, thus newly synthesized dopamine is not required for the bromocriptine-induced depressant effect (Jackson et al., 1988). Our observation that SCH 23390 and haloperidol completely blocked the stimulant effects of apomorphine and bromocriptine confirms previous reports that dopamine D_1 and D_2 receptors are clearly involved in apomorphine- and bromocriptine-induced locomotor stimulation (Jackson et al., 1988; Zarrindast and Eliassi, 1991). In the present study, Ca^{2+} channel blockers did not cause significant alteration of locomotor activity in naive mice. These results are consistent with previous findings obtained with moderate doses of Ca^{2+} channel blockers which did not affect spontaneous locomotor activity (Bourson et al., 1989; Antkiewicz-Michaluk et al., 1994a; Maiolini Junior et al., 1994). However, the present results showed that motor stimulant effects of apomorphine and bromocriptine were altered differentially by the Ca^{2+} channel blockers. Antkiewicz-Michaluk et al. (1994a) have shown that apomorphine-induced hypermotility is prevented and the stereotypy is facilitated by nifedipine in rats. This is in contrast with our findings. Species differences may account for this discrepancy and another possibility is that nifedipine exerts pharmacological actions other than Ca^{2+} channel blockade (Swanson and Green, 1986). The interaction between Ca^{2+} channel blockers and bromocriptine-induced locomotion has not been studied. The inhibition by Ca^{2+} channel blockers of bromocriptine-induced locomotor stimulation could be due to dopaminergic receptor blockade. However, since Ca^{2+} channel blockers do not inhibit apomorphine-induced stimulation, this explanation cannot be valid. Inhibition of bromocriptine-induced locomotor stimulation without alteration of bromocriptine-induced locomotor depression by Ca^{2+} channel blockers may be related to inhibition of dopamine formation, as suggested by Pileblad and Carlsson (1986). Ca^{2+} channel blockers decrease the levels of dopamine metabolites in mouse brain, indicative of inhibition of amine synthesis (Pucilowski, 1992). Additionally, Bagchi (1990) has shown that Ca^{2+} channel blockers may enhance the inactivation of dopamine present in intraneuronal vesicles, suggesting a reserpine-like action. Another possibility for the inhibition by Ca^{2+} channel blockers of the locomotor stimulation by bromocriptine may be related to protection of bromocriptine's sensitization of the dopamine D_2 receptors to endogenous dopamine (Jackson and Jenkins, 1985) by Ca^{2+} channel blockers. Some Ca^{2+} channel blockers have been found to protect against behavioral sensitization brought about by repeated exposure to dopaminergic agonists (Bedingfield et al., 1996) or neuroleptic withdrawal (Grebb et al., 1987; Mamczarz et al., 1994). In addition, high-affinity binding of bromocriptine to 5-hydroxytryptamine$_{1A}$, α_1 and α_2 adrenoceptors was reported (Jackson et al., 1995). All of these receptors have been reported to play a role in the regulation of motor function. The functional consequences of high-affinity binding of bromocriptine to these receptors is unknown. The effects of Ca^{2+} channel blockers on bromocriptine-induced locomotion may be exerted through adrenergic and serotonergic mechanisms. It has been shown that some Ca^{2+} channel blockers activate serotonergic (Gaggi et al., 1993), and facilitate adrenergic transmission (Pucilowski, 1992).

It is well known that morphine induces locomotor stimulation in mice, an effect termed 'running fit', over a wide range of doses (Rethy et al., 1971; Oliverio, 1975). Regarding the stimulant effect of morphine on locomotor activity in mice, some investigations have suggested participation of central dopaminergic systems. Our study provided evidence that both dopamine D_1 and dopamine D_2 receptors are essential for the expression of morphine-induced stimulation, in agreement with some earlier studies (Longoni et al., 1987; Zarrindast and Zarghi, 1992; Magnus-Ellenbroek and Havemann-Reinecke, 1993). Some authors have reported that, in brain dialysis studies, morphine-induced stimulation of locomotion was associated with stimulation of dopamine release in the striatum and nucleus accumbens in rats (Di Chiara and Imperato, 1986; Di Chiara and Imperato, 1988). In our work, Ca^{2+} channel blockers failed to reduce morphine-induced locomotor stimulation. This effect of morphine was decreased by dopamine receptor blockade, further confirming that the effects of calcium channel blockers on stimulant-induced hyperactivity are not related to blockade of dopamine receptors. If the stimulant effect of morphine is related to dopamine release, it appears that Ca^{2+} channel blockers are unlikely to inhibit morphine-induced dopamine release. It has been suggested Ca^{2+} channel blockers modulate amine reuptake and intraneuronal resynthesis-metabolism of neurotransmitters, rather than release (Pucilowski, 1992). Our results disagree with the findings reported by Martin et al. (1990) who have shown that nifedipine and diltiazem decrease morphine-induced hypermotility; this discrepancy could be explained by the use of higher diltiazem doses. We used diltiazem at a dose of 10 mg/kg, whereas Martin et al. (1990) used 30 mg/kg. In addition, Pavone et al. (1992) compared the effects of nifedipine with those of a non-Ca^{2+} antagonist vasodilator, hydralazine, suggesting that the interaction with morphine was not exclusively

related to neuronal changes produced by Ca^{2+} channel blockade, but also to hemodynamic factors. Higher doses of Ca^{2+} channel blockers may decrease morphine-induced hypermotility by lowering systemic blood pressure. Ca^{2+} channel blockers and morphine may produce a synergistic reduction in blood pressure, which could play a role in the reduction of locomotor activity induced by a combination of Ca^{2+} channel blockers and morphine as found in other studies (Martin et al., 1990; Pavone et al., 1992). In our previous study, amlodipine (5 mg/kg) produced a 17% reduction of blood pressure (Doğrul et al., 1997). In this study, we used amlodipine at a lower dose (2.5 mg/kg) which was not expected to appreciably alter systemic blood pressure.

In conclusion, our results demonstrated that, in mice, Ca^{2+} channel blockers interfere with bromocriptine-induced locomotor stimulation but not with the locomotor depression induced by bromocriptine. Our findings contradict the suggestion that Ca^{2+} channel blockers prevent morphine and apomorphine-induced locomotor stimulation. It would appear that dopaminergic D_1 or D_2 receptors are involved in apomorphine, bromocriptine and morphine-induced locomotion. We therefore suggest that the effects of Ca^{2+} channel blockers on the dopaminergic system appear not to be related directly to dopamine D_1 or D_2 receptor blockade.

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