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Atipamezole, an α_2-adrenoceptor antagonist, augments the effects of L-DOPA on evoked dopamine release in rat striatum

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Abstract

The effects of atipamezole, an α_2-adrenoceptor antagonist, L-3,4-dihydroxyphenylalanine (L-DOPA) and the combination of these drugs on dopamine overflow were studied in dopaminergic presynaptic terminals of rat caudate and nucleus accumbens. Dopamine overflow evoked by 100 pulses of electrical stimulation of the medial forebrain bundle at a low (20 Hz) and high (50 Hz) frequency was measured by in vivo voltammetry. L-DOPA (15 mg/kg) increased dopamine overflow in the caudate nucleus, but this dose had no effects in the nucleus accumbens. Atipamezole (300 μg/kg) had no effects on its own on dopamine overflow, but it did increase the size of the readily releasable storage pool and the effects of L-DOPA treatment in both structures. The combination of the drugs increased dopamine overflow to a larger extent at high compared to low stimulation frequencies. We conclude that the rat caudate nucleus is more sensitive than the nucleus accumbens to the effects of L-DOPA, and the effects of L-DOPA treatment might be effectively enhanced by antagonism of α_2-adrenoceptors.
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1. Introduction

It is known that specific α_2-adrenoceptor agonists may act presynaptically to decrease dopamine neurotransmission in dopaminergic terminals (Russell et al., 1993; Trendelenburg et al., 1994; Yavich et al., 1997; Bücheler et al., 2002). The presynaptic effects of α_2-adrenoceptor antagonists on dopamine overflow are less well known, and data on their effects are still controversial. Systemic injection of α_2-adrenoceptor antagonists increased the basal extracellular dopamine level in the rat cerebral cortex (Gobert et al., 1998; Matsumoto et al., 1998; Hertel et al., 1999; Devoto et al., 2001). However, this may be due to an indirect influence of the noradrenergic system on the firing rate of dopaminergic neurons (Herve et al., 1982; Grenhoff and Svensson, 1989; Lategan et al., 1990, 1992). When the direct effects of α_2-adrenoceptor agonist and antagonist on presynaptic processes were investigated, we did not find any effects of atipamezole, an α_2-adrenoceptor antagonist, in the mouse caudate and the nucleus accumbens; while medetomidine, a selective α_2-adrenoceptor agonist, blocked dopamine release under the same experimental conditions (Yavich et al., 1997). In contrast to this finding, local perfusion of idazoxan has been recently reported to increase the extracellular dopamine concentration in the rat prefrontal cortex (Yamamoto and Novotney, 1998; Devoto et al., 2001). It seems that the effects of α_2-adrenoceptor antagonists may well be site specific. There is no evidence that α_2-adrenoceptors are localized or differently distributed on dopaminergic terminals in the dopaminergic terminal fields and, thus, no reasonable explanation for the mechanisms and differences in the effects of antagonists. However, recent experimental and clinical data indicate that α_2-adrenoceptor antagonists can improve the therapeutic effects of L-3,4-dihydroxyphenylalanine (L-DOPA) and decrease L-DOPA-induced dyskinesia (Grondin et al., 2000; Fox et al., 2001; Rascol et al., 2001).

The rate of dopamine synthesis and the capacity of storage pools in the cortex, the caudate and the nucleus accumbens seem to be different (Garris et al., 1993), and it

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is known that α_2-adrenoceptor antagonists modulate synthesis of catecholamines (Esteban et al., 1996; Sastre-Coll et al., 1999) in these areas. One could hypothesize that this could represent the neurochemical basis for the effects of α_2-adrenoceptor antagonists.

The aim of the present experiment was to study the neurochemical effects of atipamezole, a specific and potent α_2-adrenoceptor antagonist (Virtanen et al., 1989; Haapalinna et al., 1997) in combination with L-DOPA on the evoked dopamine release from the terminals of the mesolimbic (nucleus accumbens) and nigrostriatal (caudate nucleus) dopaminergic systems. In vivo voltammetry was used to analyze evoked dopamine overflow following brief electrical stimulation of the medial forebrain bundle. While this approach does not allow one to measure basal levels of extracellular dopamine, it does permit distinguishing presynaptic effects of drugs from their effects on the firing rate of the dopaminergic neurons.

2. Methods

2.1. Preparation of animals

All experiments were carried out on male Wistar rats (250–350 g), bred in National Animal Centre, Kuopio, Finland. Experimental procedures were approved by the local committee on animal welfare. Rats were anaesthetized with chloral hydrate (450 mg/kg i.p.). Anaesthesia during surgery was maintained at a level sufficient to prevent corneal reflexes by repeated injections of the anaesthetic at 100 mg/kg every 40–60 min. Rectal temperature was kept at 37 ± 0.5 °C.

After removal of a small region of the skull with a dental drill and opening of the dura, a working (detector) electrode was placed according to the coordinates of rat brain atlas (Paxinos and Watson, 1986) in the nucleus accumbens core (AP: 1.6 mm, L: 1.5 mm, V: −7.0 mm vs. bregma and cortical surface) or the caudate nucleus (AP: 1.6 mm, L: 2 mm, V: −4.5 mm). A miniature silver/silver chloride reference electrode in a saline bridge was positioned on the contralateral side of the skull. The auxiliary electrode (stainless steel screw) was embedded in the occipital bone. The locations of the working electrodes were verified histologically following electrical lesions (6 V, 15 s) in the drug-treated groups. The locations of the working electrodes within the caudate and the nucleus accumbens are given in Fig. 1.

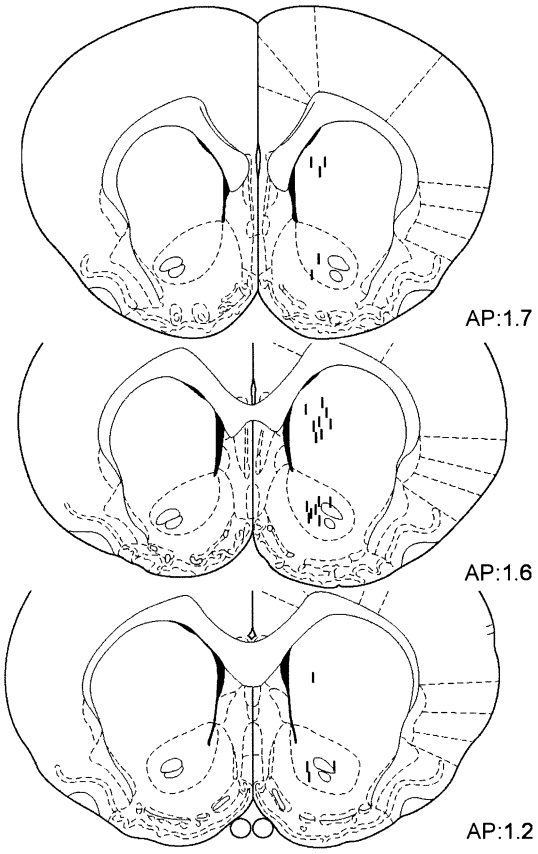

Fig. 1. The locations of the working electrodes within rat caudate and nucleus accumbens.

2.2. Electrical stimulation

A bipolar stimulating electrode with parallel tips was implanted in the medial forebrain bundle (AP: −2.0 mm, L: 2.0 mm, V: −8.5–8.9 mm vs. bregma and cortical surface). The electrode was lowered 0.5 mm above the region of interest, and stimulation started while the electrode was advanced (0.2 mm at a time). The stimulating electrode was fixed at the depth where the oxidation current at the working electrode was maximal. A Master-8 stimulator (AMPI, Israel) and battery-operated Stimulus Isolator (A365, WPI, USA) were used for electrical stimulation. A 100 constant-current bipolar pulses (2 ms each square wave) at 20 or 50 Hz, electronically switched on for the period of stimulation, were applied on the stimulating electrode. The peak current was normally kept at 200 μA. The stimulation was synchronized with voltammetric measurements to avoid artefacts.

2.3. Electrochemical technique

Fast in vivo voltammetry techniques allow one to measure evoked dopamine overflow in a very small area within dopaminergic terminal fields in ‘real time’, and it has been proposed (Stamford et al., 1988a, 1991) that when used with electrical stimulation of the dopamine ascending pathway, fast in vivo voltammetry provides the opportunity to analyze the effects of drugs solely on the presynaptic processes, without influences resulting from the effects of these drugs on the firing rate of the dopamine neurons.

The dopamine overflow following stimulation of the medial forebrain bundle was measured by chronoampero-

metry with a single Nafion-coated (Gerhardt et al., 1984) carbon fibre, 8 μm in diameter, 300 ± 50 μm long, as the working electrode. The computer-generated input waveform, which was applied to the working electrode, was a 0.0–0.5 V square pulse, 50 ms width. The catechol oxidation current was measured and integrated from 25 to 48 ms of the applied 50 ms square pulse. Current was monitored at +0.5 V vs. Ag/AgCl electrode every 0.33 s (Yavich et al., 1997). Following control experiments (injections of saline), the positions of the electrodes within the brain were not estimated since electrolytic lesions completely abolished the electrodes' sensitivity. Instead, the electrodes were calibrated with solutions of dopamine (0.5 and 1 μM) and ascorbic acid (200 μM) in 0.1 M phosphate-buffered saline (pH = 7.4).

2.4. Experimental protocol

Low (5 s, 20 Hz)- and high (2 s, 50 Hz)-frequency electrical stimulations were applied on the medial forebrain bundle at 5 min interval. These two stimulations were repeated every 20 min. When the effects of atipamezole were to be investigated, the drug was injected after the third pair of stimulation. Carbidopa was injected 20 min before L-DOPA (i.e. after the second pair of stimulation). L-DOPA was injected immediately after the third pair. In experiments involving drug combinations, atipamezole was injected 20 min before L-DOPA immediately after carbidopa injection.

Repeated high-frequency (4 s, 50 Hz) electrical stimulations were used to analyze the size of the readily releasable dopamine storage pool in the caudate nucleus. Five stimulations at 30 s intervals were applied on the medial forebrain bundle. It was shown that this rate of the stimulation induced a progressive decline in the dopamine release on each subsequent stimulation because of exhaustion of the readily releasable storage pool (Yavich and MacDonald, 2000). Atipamezole or saline was injected after the last stimulation, and five repeated stimulations were applied 20 min later. Experiments were randomised, and six rats were used for each saline control and drug-treated group.

2.5. Data presentation and statistics

The effects of the drugs were expressed as a percentage of the peak amplitude of dopamine overflow following the last stimulation recorded before drug injection. When the effects of atipamezole on the capacity of the storage pool were to be investigated, dopamine overflow was expressed as a percentage of the dopamine release following the first stimulation in series of five. Data are shown as means ± S.E.M.

Statistical analysis of the effects of drugs was performed using multivariate analysis of variance (MANOVA) for repeated measures with drug treatment as the between-subjects factor and repeated electrical stimulation and stimulation frequency (low and high) as the within-subjects factor. The stability of dopamine overflow after repeated stimulation was analyzed using multivariate test of significance (Pillai's statistics). The individual differences between results were analyzed using Scheffe multiple comparison post hoc test. The mean levels of dopamine overflow in absolute values (μmol/l) in the caudate and the nucleus accumbens were compared using *t*-test for independent samples. SPSS for Windows v.8 statistical package was used for calculations.

2.6. Drugs and chemicals

L-3,4-dihydroxyphenylalanine (L-DOPA methyl ester hydrochloride, Sigma, USA), at a dose of 15 mg/kg (dose refers to the salt), was prepared shortly before intraperitoneal injection. This drug was given in combination with carbidopa (EGIS, Hungary) at a dose of 10 mg/kg i.p. Carbidopa (free base) was also prepared freshly with a drop of TWEEN 80. In control experiments, saline, with a drop of TWEEN 80, was injected intraperitoneally (5 ml/kg). Atipamezole (Orion Pharma, Finland) was dissolved in saline and given subcutaneously (1 ml/kg).

3. Results

Saline treatment did not affect dopamine overflow; however, when all data from control experiments were combined, some trend towards a decrease of the amplitude of response due to sensitivity lost of the working electrode was seen during the experiment (within-subjects effects: 20 Hz: $F(5) = 3.348$, $P = 0.008$; 50 Hz: $F(5) = 3.391$, $P = 0.007$). In individual estimations, the trend was significant only in the caudate nucleus at the low-frequency stimulation (within-subjects effects: $F(5) = 2.954$, $P = 0.031$). No other differences were found between the control groups (between-subjects effects: $F(3) = 0.31$, $P = 0.820$).

The working electrodes, which were used in the control experiments, were calibrated in solution with dopamine and ascorbic acid after the measurements. On the basis of this postcalibration, the peak concentrations of dopamine, 20 min after saline injection, were calculated (Table 1). With

Table 1
The peak dopamine release following electrical stimulation (100 pulses) of the medial forebrain bundle in rat caudate and nucleus accumbens

Group ($n = 6$)	Frequency of stimulation (Hz)	Mean ± S.E.M. (μM)
Caudate nucleus	20	0.389 ± 0.060
	50	3.192 ± 0.458
Nucleus accumbens	20	0.371 ± 0.118
	50	2.031 ± 0.542

Stimulation, 20 Hz: $t = 0.131$, $df = 10$, $P = 0.899$; caudate nucleus vs. nucleus accumbens.
Stimulation, 50 Hz: $t = 1.635$, $df = 10$, $P = 0.134$; caudate nucleus vs. nucleus accumbens.

the same amount of pulses employed, dopamine overflow at the high-frequency stimulation was about 10 times larger than at the low-frequency stimulation. There were no differences between the caudate and the nucleus accumbens in the evoked dopamine overflow following low- or high-frequency stimulation of the medial forebrain bundle.

L-DOPA (15 mg/kg, i.p.), in combination with carbidopa, increased dopamine release in the caudate nucleus following low (Fig. 2A; L-DOPA vs. saline: $P=0.013$)-and high (Fig. 2B, L-DOPA vs. saline: $P=0.004$)-frequencies of stimulation. The maximal increase of about 40% was seen 40–60 min after administration and it disappeared at the end of the observation period. L-DOPA had no effects on dopamine overflow in the nucleus accumbens (Fig. 3A,B) at either frequency of stimulation.

Atipamezole (300 μg/kg, s.c.) given alone had no effects on the evoked dopamine overflow at either frequency of stimulation in the caudate nucleus (Fig. 2A,B; multivariate test, treatment × time after injection × stimulation frequency: $F(5,6)=0.014$, $P=0.907$) or in the nucleus accumbens (Fig. 2A,B; $F(5,6)=0.634$, $P=0.683$). Atipamezole increased the effects of L-DOPA on dopamine overflow in the caudate nucleus at both stimulation frequencies (Fig. 2A; 20 Hz, drug combination vs. L-DOPA: $P=0.007$; 50 Hz: $P=0.001$). The effects of drug combination at the high frequency of stimulation were larger than following stimulation at the low frequency (test of within-subjects contrasts, treatment × time after injection × stimulation frequency: $F(3)=3.272$, $P=0.043$).

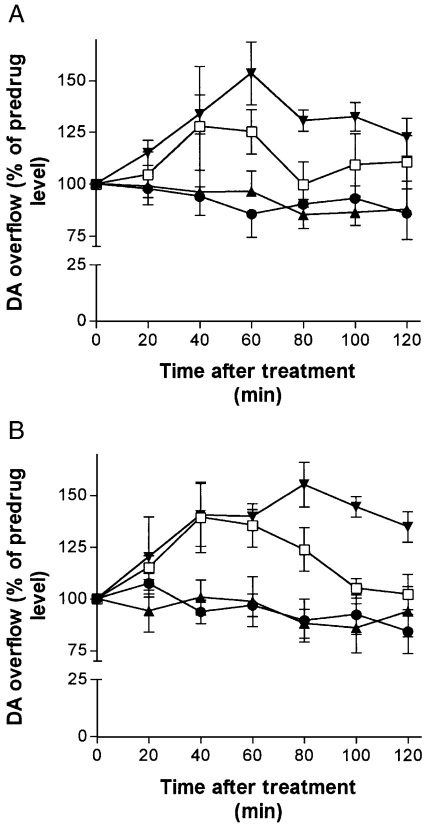

Fig. 2. The effects of L-DOPA and atipamezole treatment on the evoked dopamine overflow in the caudate nucleus following the low (A) and the high (B) frequencies of stimulation of the medial forebrain bundle. Peak dopamine overflow is expressed as a percentage of the peak overflow before administration of drug or saline. Each point represents the mean ± S.E.M. obtained in six rats. Saline (●), L-DOPA (□, 15 mg/kg i.p.), atipamezole (▲, 300 μg/kg s.c.), or their combination (▼) were injected immediately after the stimulation at time 0.

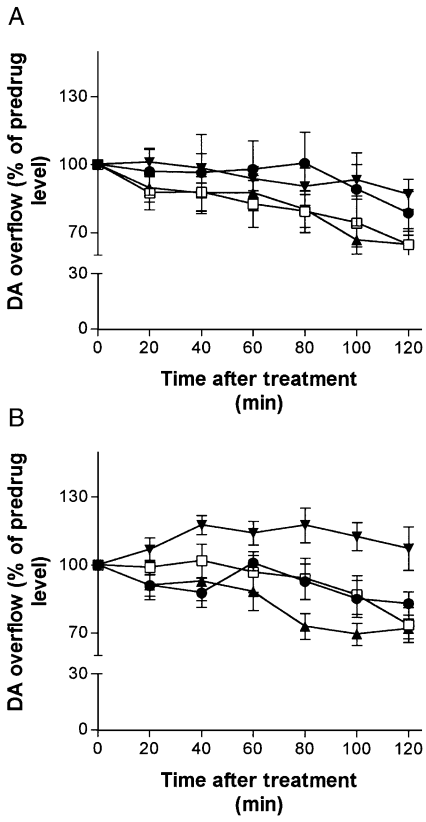

Fig. 3. The effects of L-DOPA and atipamezole treatment on the evoked dopamine overflow in the nucleus accumbens following the low (A) and the high (B) frequencies of stimulation of the medial forebrain bundle. Peak dopamine overflow is expressed as a percentage of the peak overflow before administration of drug or saline. Each point represents the mean ± S.E.M. obtained in six rats. Saline (●), L-DOPA (□, 15 mg/kg i.p.), atipamezole (▲, 300 μg/kg s.c.), or their combination (▼) were injected immediately after the stimulation at time 0.

This dependence on frequency became even more evident in the nucleus accumbens where the effects of saline, atipamezole, L-DOPA and the combination of atipamezole with L-DOPA did not change dopamine overflow at a low-frequency stimulation (Fig. 3A; overall test of between-subjects effects (treatments): $F(3)=0.937$, $P=0.441$). The combination of L-DOPA with atipamezole significantly increased evoked dopamine overflow at the high-frequency stimulation to about 20% of control (saline) level (Fig. 3B; overall test of between-subjects effects: $F(3)=6.256$, $P=0.004$; drug combination vs. saline: $P=0.001$).

Five consecutive, repeated at 30 s, stimulations gradually decreased dopamine overflow (Fig. 4, insert). Saline had no effects on the dynamics of the dopamine decline, while

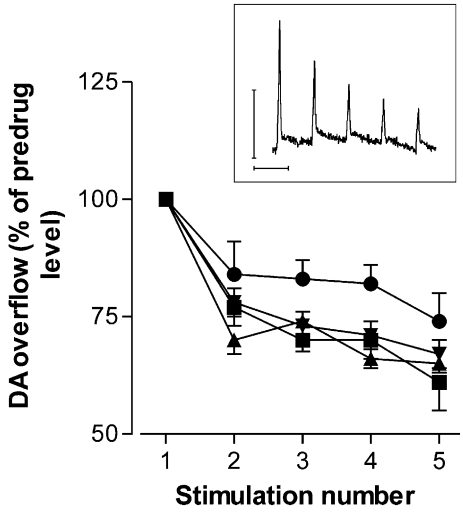

Fig. 4. The effects of atipamezole on the readily releasable dopamine storage pool. Repeated high-frequency electrical stimulations of the medial forebrain bundle were used to exhaust the readily releasable storage pool. Saline (▼) or atipamezole (●, 300 μg/kg s.c.) was injected immediately after the first five repeated at 30 s stimulation (■—control stimulations, before injection of saline; ▲—control stimulations, before injection of atipamezole) and the results of treatment were tested 20 min later following the second burst of five repeated stimulations. Dopamine overflow is expressed as a percentage of the dopamine release following the first stimulation in series of five. Data shown as means ± S.E.M. Insert—example of voltammetric recordings demonstrating dopamine decline following five stimulations at 30 s intervals. Scale bars are 0.2 nA and 30 s.

atipamezole (300 μg/kg, s.c.) significantly inhibited the dopamine decline in the caudate nucleus (Fig. 4; multivariate test, treatments: $F(3,32) = 74.5$, $P = 0.001$).

4. Discussion

We investigated the effects of atipamezole at 300 μg/kg and L-DOPA at 15 mg/kg alone and in combination on the evoked dopamine overflow from the terminal fields in the rat caudate and the nucleus accumbens. To our knowledge, this is the first report that has employed in vivo voltammetry to examine the effects of this relatively small, but behaviourally relevant dose of L-DOPA. L-DOPA increased dopamine overflow in the caudate nucleus, but did not change it in the nucleus accumbens. Atipamezole had no effects on its own on dopamine overflow induced by single stimulation, but it inhibited dopamine decline induced by repeated stimulation of the medial forebrain bundle and in combination with L-DOPA, atipamezole increased dopamine overflow in both structures. This effect was frequency dependent.

Dopamine overflow in the terminal fields induced by a brief electrical stimulation of ascending pathways merely reflects the processes of release and re-uptake. The extracellular dopamine that is registered by a working electrode is the sum of these two processes, which has been suggested to follow Michaelis–Menten kinetics (May et al., 1988; Wightman et al., 1988). The concentrations of extracellular dopamine following an identical stimulation pattern of the medial forebrain bundle were the same in the caudate and the nucleus accumbens after injections of saline; however, there is less re-uptake of dopamine in the nucleus accumbens (Stamford et al., 1988b; Jones et al., 1995a,b). Thus, to maintain the same extracellular concentration of dopamine in both structures following an identical stimulation of the medial forebrain bundle, release per pulse of stimulation has to be smaller in the nucleus accumbens. The same conclusion was made recently on the basis of experimental work (Wu et al., 2001). This may explain the different sensitivity of these two structures to the effects of L-DOPA, since L-DOPA increases release of dopamine per pulse of stimulation (Wightman et al., 1988).

The present work employed low and high frequencies of stimulation with the same amount of stimulation pulses (100 pulses). This approach allows one to separate the effects of drugs on the processes of release and re-uptake. An increase in the frequency of stimulation disrupts the balance between release and re-uptake and elevates extracellular concentration of dopamine (May et al., 1988; Wightman et al., 1988). If atipamezole or its combination with L-DOPA was to have any effect on dopamine re-uptake, we should be able to discern these effects at a low stimulation frequency. This is because 20 Hz stimulation evoked a low extracellular concentration of dopamine, which was about 0.4 μM according to our postcalibration data. This value is more comparable with K_m for dopamine re-uptake (about 0.2 μM) than the amount of dopamine released following the high-frequency stimulation (2–3 μM). However, we observed that the effects of combination of L-DOPA with atipamezole increased as the stimulation frequency increased. Direct comparison of the shapes of voltammetric signals, which reflect dynamics of dopamine release and re-uptake in real time, also did not show any changes in the dopamine re-uptake (data not shown). Thus, we conclude that atipamezole influenced the effects of L-DOPA on dopamine release without affecting the re-uptake processes.

Our results are in agreement with the recent finding that idazoxan, another α_2-adrenoceptor antagonist, increased methylphenidate and apomorphine-induced rotation in 6-hydroxydopamine-lesioned rats; although, idazoxan did not cause any circling behaviour on its own (Chopin et al., 1999). The effects of atipamezole on L-DOPA and amphetamine-induced turning behaviour in hemiparkinsonian rats were also recently tested (Huotari et al., 2000). Atipamezole moderately enhanced L-DOPA-induced contralateral and amphetamine-induced ipsilateral turning. This similarity in behavioural and neurochemical effects of α_2-adrenoceptor antagonists is not conclusive evidence that the facilitation of circling behaviour is due exclusively to enhanced dopamine release. However, this mechanism is a very plausible explanation for the effects of methylphenidate, amphetamine and L-DOPA.

There is no evidence that α_2-adrenoceptors are localized on dopaminergic terminals. α_{2A}- and α_{2C}-adrenoceptors subtypes are found in the cortex and striatum, and it was recently shown that α_{2C}-adrenoceptors, which dominate in striatum (Scheinin et al., 1994), are localized on the GABAergic medium-sized spiny projection neurons (Holmberg et al., 1999). These two receptor subtypes determine the presynaptic inhibitory effects of α_2-adrenoceptor agonists on noradrenaline and dopamine release (Trendelenburg et al., 2001; Bücheler et al., 2002; Ihalainen and Tanila, 2002). However, the results of present work with α_2-adrenoceptor antagonist and L-DOPA cannot be similarly explained. The differences between the effects of idazoxan in the cortex (Yamamoto and Novotney, 1998; Devoto et al., 2001) and atipamezole in striatum (Yavich et al., 1997) indicate that noradrenergic tone in striatum is very low. This is also confirmed by known very low adrenergic innervation of striatum. There are data that α_2-adrenoceptor antagonists can modulate the synthesis of catecholamines (Esteban et al., 1996; Sastre-Coll et al., 1999). Dopamine recently synthesized from L-DOPA forms the readily releasable storage pool, which releases dopamine on neuronal activation or electrical stimulation (see Yavich and MacDonald, 2000 for more references). Our data, that atipamezole inhibited dopamine decline following repeated stimulation, which is known to exhaust the readily releasable dopamine storage, indicate that atipamezole intensified dopamine accumulation in the releasable pool and increased its size. This neurochemical effect of atipamezole is synergistic with the effects of L-DOPA, which is the source of dopamine for the readily releasable storage pool and may account for the increase in dopamine overflow when two drugs are combined.

The combination of L-DOPA with atipamezole selectively increased dopamine overflow at the low stimulation frequency in the caudate nucleus. The low stimulation frequency, which was used in the present work, is close to the physiological range of bursting of dopamine neurons. Thus, the enhanced effects of L-DOPA on dopamine release following combination with an α_2-adrenoceptor antagonist may be beneficial for the treatment of Parkinson's disease.

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