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ATP-sensitive K^+ channel openers block sulpiride-induced dopamine release in the rat striatum

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Abstract

In vivo brain microdialysis was used to investigate the role of ATP-sensitive K^+ (K_{ATP}) channel openers in dopamine release regulated by dopamine autoreceptors in the rat striatum. Local infusion of two K_{ATP} channel openers, nicorandil (10^{-5}–10^{-3} M) and cromakalim (10^{-5}–10^{-3} M), into the striatum thorough the dialysis membrane produced dose-dependent decreases in extracellular concentrations of dopamine. Local application of the dopamine D_2 receptor antagonist, (−)-sulpiride (10^{-5} M), produced significant increases in extracellular concentrations of dopamine. Both nicrorandil (10^{-5} M) and cromakalim (10^{-4} M) blocked significantly (−)-sulpiride (10^{-5} M)-induced increases in dopamine levels in the striatum. These results suggest that activation of K_{ATP} channels in the striatum causes decreases in endogenous dopamine release in vivo. Furthermore, the sulpiride-induced increases in dopamine levels caused by blocking the tonic activation of dopamine autoreceptors were inhibited by activation of K_{ATP} channel. These data indicate that K_{ATP} channels may be present in nigrostriatal dopaminergic terminals and that striatal dopamine autoreceptors inhibit dopamine release tonically by activation of K_{ATP} channels.

Keywords: ATP-sensitive K^+ channel; Nicorandil; Cromakalim; Dopamine autoreceptor; Microdialysis; Sulpiride

1. Introduction

ATP-sensitive K^+ (K_{ATP}) channels are closed by intracellular ATP (Noma, 1983) and are found in pancreatic β-cells (Ashcroft, 1988) and cardiac muscle (Noma, 1983). Recent binding studies show that K_{ATP} channels are widely distributed in the central nervous systems (Mourre et al., 1989; Gehlert et al., 1991) including the substantia nigra (Mourre et al., 1989; Treherne and Ashford, 1991), hippocampus (Mourre et al., 1989) and motor neocortex (Mourre et al., 1989). Closing of K_{ATP} channels causes depolarization, which leads to insulin release from pancreatic β-cells (Schmid-Antomarchi et al., 1987). Opening of K_{ATP} channels relaxes smooth muscle by increasing K^+ conductance, which results in hyperpolarization (Hamilton and Weston, 1989). However, little is known about the role of K_{ATP} channels in the central nervous system.

Somatodendritic dopamine autoreceptors in the substantia nigra appear to produce membrane hyperpolarization and reduce firing by activating an outward K^+ current (Lacey et al., 1987, 1988), however, the precise identity of this K^+ channel is not known. Roeper et al. (1990) reported that tolbutamide, which blocks K_{ATP} channels (Ashford et al., 1990), blocked dopamine D_2 receptor agonist-induced membrane hyperpolarization in substantia nigra neurons in vitro. In contrast, it has been reported that the K_{ATP} channel blocker, glibenclamide, does not antagonize dopamine-induced hyperpolarization and that the K_{ATP} channel opener, cromakalim, has no effect on dopaminergic neurons in the substatia nigra, suggesting that dopamine D_2 receptors are not coupled to K_{ATP} channels (Hicks and Henderson, 1992).

The purpose of this study is to investigate the role of K_{ATP} channels in dopamine autoreceptor function in nigrostriatal dopaminergic nerve terminals using the in vivo microdialysis technique.

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2. Materials and methods

2.1. In vivo microdialysis

All animal procedures were performed in accordance with the Guiding Principles for The Care and Use of Animals in The Field of Physiological Sciences (The Physiological Society of Japan) and were approved by the Committee of Animal Experimentation, Kurume University School of Medicine. Male Wistar rats (body weight 260–350 g) were anesthetized (sodium pentobarbital, 50 mg/kg, i.p.) and stereotaxically implanted with a U-shaped microdialysis probe in the right striatum. The coordinates for placement of the tip of the probes were AP +0.5, ML 3.0, DV 6.5 for the striatum according to bregma and to the brain surface (according to the atlas of Paxinos and Watson, 1986). The active region of the cellulose hollow dialysis tube (0.25 mm diameter; molecular weight cut off 50000) was 5 mm in length. All experiments were carried out 1 or 2 days after the implantaion of the dialysis probe, on freely moving, conscious rats during the light phase of the day/night cycle.

The rat was connected directly to the high-performance liquid chromatographic (HPLC) equipment for on-line analysis of dopamine (EICOM Co, Kyoto, Japan). The dialysis tube was perfused with a solution (NaCl 140 mM, KCl 3.35 mM, $MgCl_2$ 1.15 mM and $CaCl_2$ 1.26 mM, pH 7.4) at a flow of 2.5 m l/min using a microperfusion pump. The dialysis sample (50 ml) was injected every 20 min via an autoinjecter (EICOM AS-10).

The mobile phase consisted of 0.1 M sodium acetate, 0.1 mM EDTA, 0.7 mM octanesulfonic acid and 10% methanol at pH 4.0. Dopamine was separated on an Eicompack MA-ODS column (4.6 mm O.D., 3.6 mm I.D. × 150 mm). The graphite working electrode was set at +600 mV vs. an Ag/AgCl reference electrode (EICOM ECD-100 electrochemical detector) and the flow rate (EICOM EP-10 pump) was 0.9 ml/min. The detection limit of dopamine was about 0.5 pg/20 min. An integrator (Chromatocorder 12, SIC, Hachioji, Japan) was used to record the signal. After a stable baseline was obtained, all drugs were added to the perfusion fluid. The average of three baseline samples immediately preceding drug perfusion was defined as 100% and all subsequent measures were related to these values (% changes). Differences between the baseline dialysate concentrations and the drug-infused samples were analyzed by one-way analysis of variance with the Newman-Keuls test. In experiment 2, during perfusion with nicorandil or cromakalim alone for 1 h, dopamine values became stable again. For this reason, the three samples from the nicorandil or cromakalim infusion period were regarded as the appropriate baseline and defined as 100% (Fig. 5). The effects of nicorandil or cromakalim on (−)-sulpiride-induced dopamine release were analyzed by two-way analysis of variance with the Newman-Keuls test. Comparison between the effects of nicorandil and cromakalim on dopamine levels was analyzed by Student's *t*-test.

2.2. Experiment 1: effect of local application of K_{ATP} channel openers and a dopamine D_2 receptor antagonist on extracellular concentrations of dopamine

After a stable baseline was obtained, the K_{ATP} channel opener, nicorandil or cromakalim, was continuously infused through the dialysis probe at concentrations of 10^{-5}–10^{-3} M for 1 h. The dopamine D_2 receptor antagonist, (−)-sulpiride (10^{-5} M), was added to the perfusion solution for 1 h after a stable baseline was obtained.

2.3. Experiment 2: effect of local application of K_{ATP} channel openers on sulpiride-induced changes in dopamine

After perfusion with nicorandil (10^{-5} M) or cromakalim (10^{-4} M) for 1 h, (−)-sulpiride (10^{-5} M) was coinfused with nicorandil or cromakalim for a further 1 h.

3. Results

After a stable baseline was obtained, the basal extracellular dopamine level became stable for the entire experimental observation period (4 h). The mean basal extracellular dopamine level detected in all animals used in these experiments ($n = 21$) was 21.4 ± 3.8 pg/20 min.

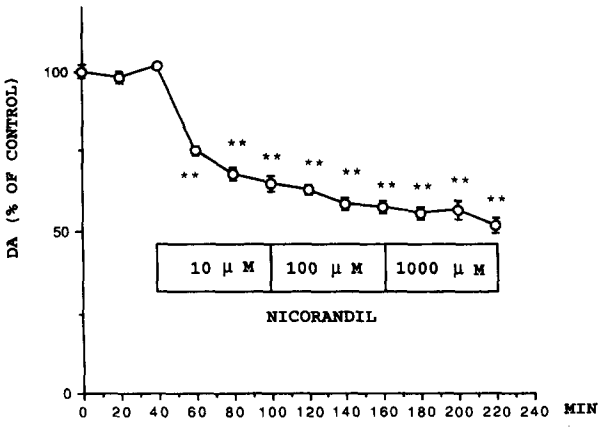

Fig. 1. Effect of various doses of nicorandil (NIC) on extracellular concentrations of dopamine in the striatum. NIC was perfused through the dialysis membrane. NIC produced a dose-dependent decrease in extracellular concentrations of dopamine. Each point represents the mean ± S.E.M. ($n = 4$). ** $P < 0.01$ compared to basal values. (one-way ANOVA and the Newman-Keuls test).

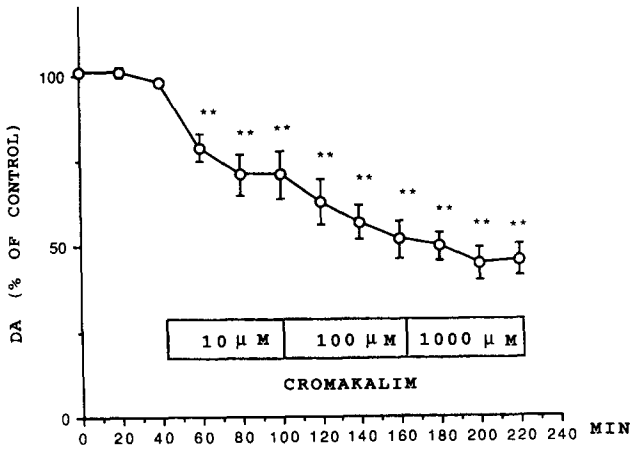

Fig. 2. Effect of various doses of cromakalim (CRM) on extracellular concentrations of dopamine in the striatum. CRM was perfused through the dialysis membrane. CRM produced a dose-dependent decrease in extracellular concentrations of dopamine. Each point represents the mean ± S.E.M. ($n = 4$). * $P < 0.05$, ** $P < 0.01$ compared to basal values. (one-way ANOVA and the Newman-Keuls test).

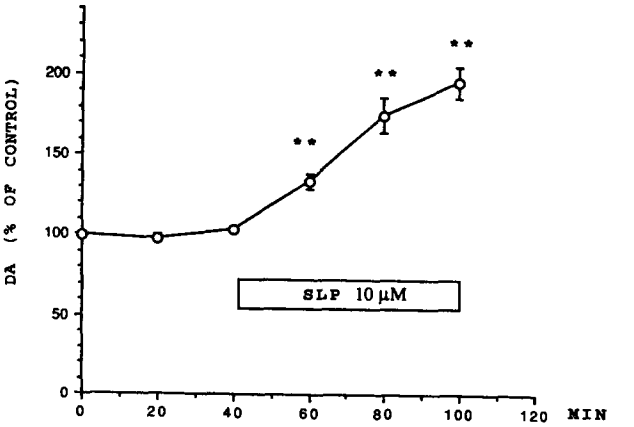

Fig. 4. Effect of (−)-sulupiride (SLP) (10^{-5} M) on extracellular concentrations of dopamine in the striatum. SLP (10^{-5} M) was perfused through the dialysis membrane for 1 h. SLP produced a significant increase in extracellular concentrations of dopamine. Each point represents the mean ± S.E.M. ($n = 5$). ** $P < 0.01$ compared to basal values. (one-way ANOVA and the Newman-Keuls test).

3.1. Effect of nicorandil, cromakalim and sulpiride on dopamine release

Local application of nicorandil or cromakalim (10^{-5} M–10^{-3} M) produced a decrease in extracellular dopamine concentrations in a dose-dependent manner. The maximum decrease in dopamine concentration was to 52% of the baseline at 10^{-3} M nicorandil (Figs. 1 and 3). Perfusion of cromakalim (10^{-5} M–10^{-3} M) also induced a significant inhibition of dopamine release in a dose-dependent manner. The maximum decrease in dopamine concentration was obtained at 10^{-3} M cromakalim perfusion (42% of baseline) (Figs. 2 and 3). At 10^{-4} M and10^{-3} M, cromakalim inhibited dopamine release more potently than nicorandil (Fig. 3).

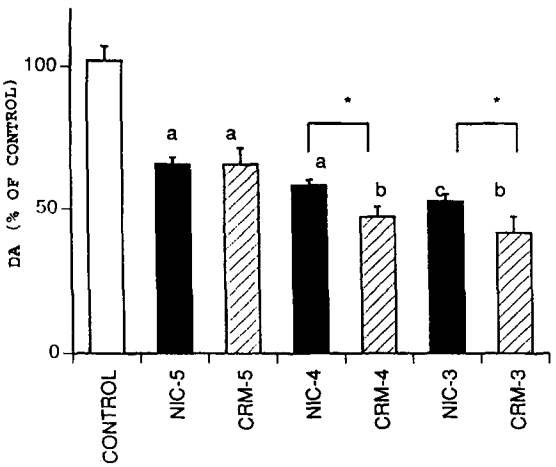

Fig. 3. Comparison of the effect of nicorandil (NIC) and cromakalim (CRM) on extracellular concentrations of dopamine in the striatum. Drugs were perfused through the dialysis membrane. At 10^{-4} M and 10^{-3} M, CRM inhibited dopamine release more potently than NIC. Only the maximum decrease in dopamine is given. open bar: control, shaded bar: NIC, hatched bar: CRM-5: 10^{-5} M, CRM-4: 10^{-4} M, CRM-3: 10^{-3} M. [a] $P < 0.05$ vs. CONTROL (one-way ANOVA and the Newman−Keuls test). [b] $P < 0.01$ vs. CRM (10^{-5} M) (Student's t-test). [c] $P < 0.05$ vs. NIC (10^{-5} M) (Student's t-test). * $P < 0.05$ (Student's t-test), NIC ($n = 4$), CRM ($n = 4$).

Local infusion of sulpiride (10^{-5} M) increased dopamine levels gradually and the maximum increase in dopamine was found in the last sulpiride perfusion sample (205%, Fig. 4).

3.2. Effect of nicorandil and cromakalim on sulpiride-induced changes in dopamine release

Coadministration of nicorandil (10^{-5} M) or cromakalim (10^{-4} M) with sulpiride (10^{-5} M) completely blocked the sulpiride-induced increase in dopamine release in the striatum (Fig. 5).

4. Discussion

There are several reports concerning the mechanism by which K^+ channels modulate the function of dopamine autoreceptors in vitro (Lacey et al., 1987, 1988; Roeper et al., 1990; Hicks and Henderson, 1992). Most of the regions investigated were dopamine cell body sites that were studied with the patch clamp technique, because this technique can be used for cell body sites, but not for nerve terminal sites. The in vivo microdialysis technique can be used in both dopamine cell body sites and dopaminergic nerve terminals (Kalivas and Duffy, 1991; Santiago and Westerink,

1991; Westerink et al., 1992; Yoshida et al., 1993) and we can evaluate presynaptic dopamine autoreceptor function in vivo using this procedure (Imperato and Di Chiara, 1988; Westerink and De Vries, 1989; Tanaka et al., 1992). In vivo microdialysis is also a useful technique for applying small quantities of drugs to restricted brain regions (Nomikos et al., 1990).

The present study is the first to indicate that intrastriatal administration of two K_{ATP} channel openers (Yanagisawa et al., 1990), nicorandil and cromakalim,

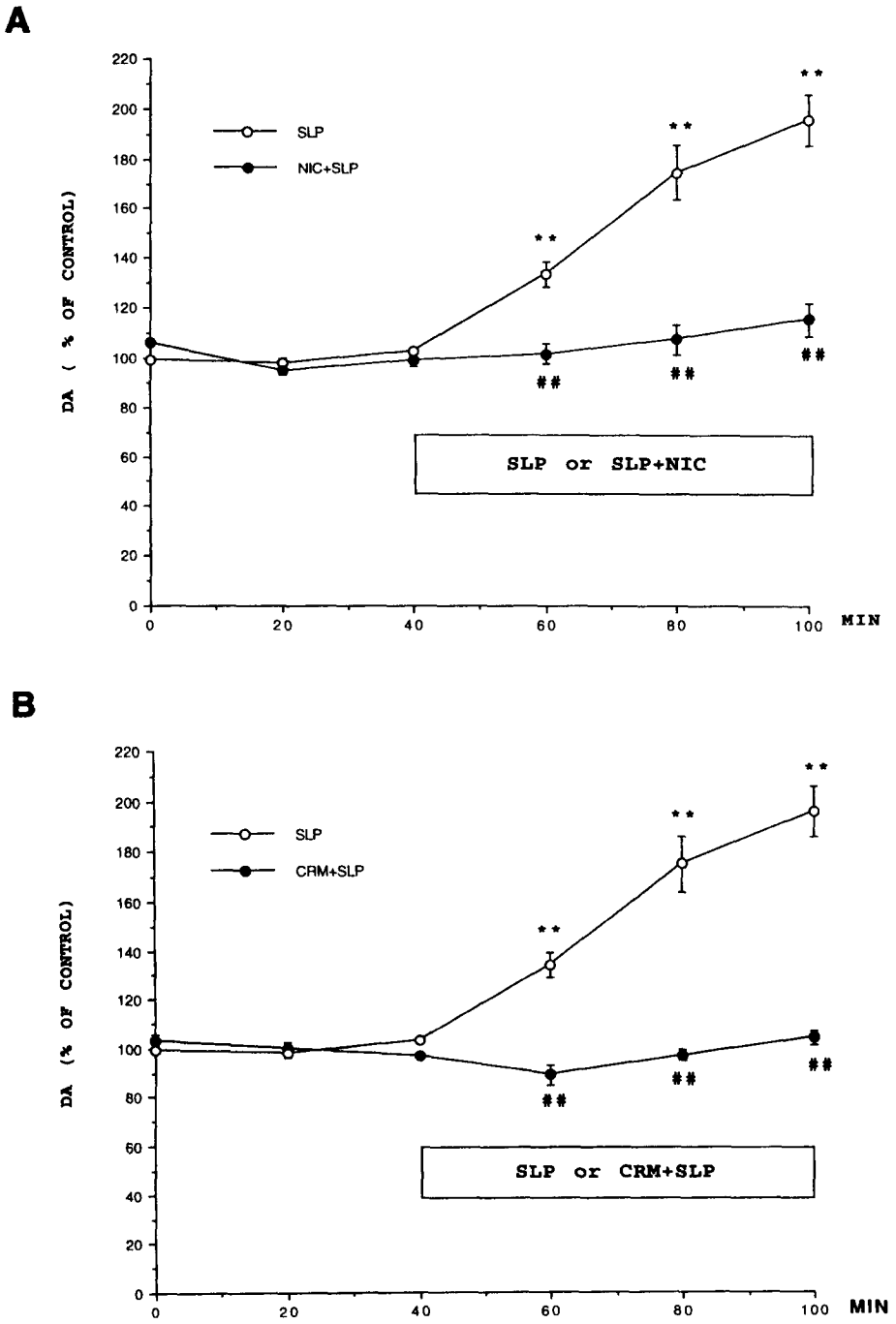

Fig. 5. Effect of nicorandil (NIC, 10^{-5} M) (A) and cromakalim (CRM, 10^{-4} M) (B) on (−)-sulupiride (SLP, 10^{-5} M)-induced increases in dopamine in the striatum. NIC (10^{-5} M, $n = 4$) or CRM (10^{-4} M, $n = 4$) was dialyzed into the striatum for 1 h, and then SLP (10^{-5} M) was added together with NIC or CRM for 1 h. Both NIC and CRM blocked SLP-induced increases in dopamine release completely. Each point represents the mean ± S.E.M. Open circle: SLP, closed circle: SLP + NIC or SLP + CRM. ** $P < 0.01$ compared to basal values. (one-way ANOVA and the Newman-Keuls test). $^{\#\#}$ $P < 0.01$ vs. SLP (two-way ANOVA and the Newman-Keuls test).

produced dose-dependent decreases in extracellular dopamine levels in the striatum in vivo.

There are some possible mechanisms whereby intrastriatal infusion of K_{ATP} channel openers produce a decrease in extracellular dopamine level in the striatum. Cromakalim causes a large hyperpolarizaiton of dissociated rat substantia nigra neurons (Hausser et al., 1991) and the hyperpolarization produced by the dopamine D_2 receptor agonist, quinpirole, is mediated by activation of K_{ATP} channels in substantia nigra neurons in the guinea pig (Roeper et al., 1990). Therefore, one possibility is that nicorandil and cromakalim produce hyperpolarization and shorten the duration of action potentials by opening K_{ATP} channels, both of which lead to a reduction in Ca^{2+} influx through voltage-dependent Ca^{2+} channels. Thus, nicorandil and cromakalim inhibit exocytotic dopamine release from nigrostriatal dopaminergic nerve terminals (Takata et al., 1992). Another possibility is that both nicorandil and cromakalim decrease dopamine release by decreasing Ca^{2+} release from intracellular stores (Yamagishi et al., 1992). The other possibility is that both nicorandil and cromakalim may directly close voltage-dependent Ca^{2+} channels by hyperpolarization and a decrease in the influx of extracellular Ca^{2+} (Yanagisawa et al., 1990), which then decreases exocytotic dopamine release in the striatum. It is also possible that local perfusion of K_{ATP} channel openers into the striatum produces activation of K_{ATP} channels, which could cause presynaptic inhibition of dopamine release by preventing propagation of action potentials from the point of excitation to the transmitter release site (propagation block) or by indirect modulation of Ca^{2+} entry (North and Williams, 1983). It has also been reported that K_{ATP} channel openers directly or indirectly reduce the affinity of the ATP-regulated site, which would result in channel opening (Fan et al., 1990). If the K_{ATP} channel is located presynaptically, then the opening of this channel serves to reduce transmitter release (Zoltay and Cooper, 1990).

Intrastriatal infusion of the dopamine D_2 receptor antagonist, sulpiride, produced increases in extracellular dopamine concentrations. This result is consistent with previous in vivo microdialysis studies (Imperato and Di Chiara, 1988; Westerink and De Vries, 1989). The mechanism by which sulpiride increases dopamine release is that sulpiride inhibits presynaptic release-modulating dopamine autoreceptors in the striatum (Westerink and De Vries, 1989). The present study indicates that sulpiride-induced increases in dopamine release are completely blocked by nicorandil and cromakalim infusion. This finding suggests that inhibition of presynaptic dopamine autoreceptors by sulpiride is blocked by activation of K_{ATP} channels in the striatum. Roeper et al. (1990) has reported that tolbutamide, which blocks K_{ATP} channels (Amoroso et al., 1990), reverses quinpirole (dopamine D_2 receptor agonist)-induced membrane hyperpolarization. Together with this report, our findings indicate that presynaptic dopamine autoreceptors in the striatum decrease dopamine release through activation of K_{ATP} channels in the nigrostriatal dopaminergic nerve terminals. These results confirm other in vitro studies showing that dopamine D_2 receptors are coupled to K_{ATP} channels (Roeper et al., 1990; Hausser et al., 1991).

Sulfonylureas act as specific inhibitors of K_{ATP} channels (Ashcroft and Ashcroft, 1990). Sulpiride is reported to produce a 90% inhibition of the binding of [^{3}H]glyburide, which is the most potent of the sulfonylureas (Schmid-Antomarchi et al., 1987), in the rat brain cortex (Ben-Ari et al., 1992). Sulpiride is a sulfonamide and its structural similarity to sulfonylureas might account for the inhibition of binding (Edwards and Weston, 1993). Blockade of K^+ channels increases the release of neurotransmitter (Bowman, 1982; Tanaka et al., 1992). Thus K_{ATP} channel openers affect these binding sites and inhibit the effect of sulpiride on dopamine release.

We reported that local application of the K^+ channel blocker, quinine, in the striatum produced a dose-dependent increase in dopamine release in this region. However, quinine does not block dopamine receptor agonist-induced decreases in dopamine release (Tanaka et al., 1992). These results indicate that dopamine D_2 receptors in the striatum do not appear to be coupled to quinine-sensitive K^+ channels and the precise identity of these K^+ channels is not fully known, since quinine has been reported as a non-selective K^+ channel blocker (Rudy, 1988). This previous report partly appears to be inconsistent with the present conclusion. The main reason for this is differences in the drugs and the combination of the drugs used in the experiments: non-selective K^+ channel blocker (Rudy, 1988), quinine, vs. dopamine D_2 receptor agonists and selective ATP-sensitive K^+ channel openers vs. dopamine D_2 receptor antagonist. Though it is not yet clear how K_{ATP} channel openers affect the action of dopamine and sulpiride-induced increases in dopamine release, the problem could be solved through studies with other selective K_{ATP} channel blockers or openers applied in combination with other dopamine D_2 receptor antagonists or D_2 receptor agonists, respectively.

Binding sites for [^{3}H]glibenclamide, which binds with high selectivity to K_{ATP} channels of central nervous system neurons (Bernardi et al., 1988), are widely distributed through the brain (Mourre et al., 1989; Gehlert et al., 1991). For example, K_{ATP} channels are present in the substantia nigra (Mourre et al., 1989), cerebral cortex (Ashford et al., 1988; Ohno and Yamamoto, 1992), hypothalamus (Ashford et al., 1990), locus coeruleus (Finta et al., 1993), thalamus (Zini et al., 1993) and caudate-putamen (Zini et al., 1993). We

have previously reported that local application of quinine, which has been recently regarded as a K_{ATP} channel blocker (Fatherazi and Cook, 1991), produced a dose-dependent increase in dopamine release (Tanaka et al., 1992) and quinine-induced increases in dopamine release in the striatum are blocked by nicorandil (Tanaka et al., 1994). Moreover, the present study demonstrates that local infusion of K_{ATP} channel openers produced a dose-dependent decrease in dopamine release. These findings strongly suggest that K_{ATP} channels exist in the rat striatum and that inhibition or activation of K_{ATP} channels in this region increases or decreases dopamine release in vivo, respectively. These results are consistent with the findings of autoradiographic studies (Zini et al., 1993) and in vitro electrophysiological studies (Cass and Zahniser, 1990, 1991; Amoroso et al., 1990; Roeper et al., 1990; Schmid-Antomarchi et al., 1990).

K_{ATP} channel openers reduce glusose-induced insulin secretion by opening K_{ATP} channels in mouse pancreatic β-cells and cromakalim inhibits insulin secretion more potently than nicorandil (Garrino et al., 1989).

The present results reveal that cromakalim inhibited dopamine release more potently than nicorandil at concentrations of 10^{-4} M and 10^{-3} M. Therefore, this finding may indicate that cromakalim is more potent than nicorandil to open K_{ATP} channels coupled to dopamine autoreceptors in vivo.

In conclusion, intrastriatal infusion of the K_{ATP} channel openers, nicorandil and cromakalim, decreased dopamine release in a dose-dependent manner in the rat striatum. Both nicorandil and cromakalim blocked sulpiride-induced increases in extracellular dopamine levels in vivo. These results suggest that K_{ATP} channels exist in the rat striatum and that release-modulating dopamine autoreceptors inhibit dopamine release through activation of K_{ATP} channels in vivo.

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