Brain Research, 367 (1986) 230–237
Elsevier

BRE 11508

Autoreceptor-Mediated Changes in Dopaminergic Terminal Excitability: Effects of Potassium Channel Blockers

JAMES M. TEPPER[1], STEVEN F. SAWYER[2], STEPHEN J. YOUNG[1] and PHILIP M. GROVES[1]

Departments of [1]Psychiatry (M-003) and [2]Neuroscience (M-008), School of Medicine, University of California, San Diego, La Jolla, CA 92093 (U.S.A.)

(Accepted July 9th, 1985)

Key words: dopamine — autoreceptor — transmitter release — 4-aminopyridine — tetraethylammonium

The effects of the potassium channel blockers, 4-aminopyridine (4-AP) and tetraethylammonium (TEA), on autoreceptor-mediated changes in dopaminergic terminal excitability were examined in urethane-anesthetized rats. Local infusions of 4-AP or TEA into neostriatal terminal fields of nigral dopaminergic neurons led to marked decreases in terminal excitability, as measured by the increase in stimulating current required to activate the neurons antidromically from the site of the infusion. The decreased excitability resulting from 4-AP could be reversed by subsequent i.v. injection of haloperidol, and was blocked in rats that had been depleted of endogenous dopamine by prior treatment with alpha-methyl-*p*-tyrosine (AMpT). Thus, the decrease in excitability elicited by the potassium channel-blockers was indirect, and apparently due to increased autoreceptor stimulation resulting from enhanced transmitter release. In addition, co-infusion of 4-AP and apomorphine in AMpT-treated animals led to decreased terminal excitability that did not differ from the effects of apomorphine alone, indicating that 4-AP did not block the effects of exogenous autoreceptor agonist administration. These results provide in situ electrophysiological evidence that autoreceptor-mediated processes occurring at dopaminergic terminals are not mediated by 4-AP- or TEA-sensitive potassium channels. Furthermore, our findings suggest that, as in other types of presynaptic terminals, blockade of voltage-sensitive potassium channels in dopamine terminals leads to enhanced release of transmitter.

INTRODUCTION

The amount of transmitter released from monoamine terminals following presynaptic depolarization has been hypothesized to be subject to feedback inhibition via the stimulation of presynaptic autoreceptors, located on or near to the sites of transmitter release[4,6,8,13,26]. Although the precise mechanism by which autoreceptor stimulation leads to a decrease in transmitter release is not well understood, recent data have indicated that the inhibition of release is associated with a decrease in the excitability of monoamine terminals to electrical stimulation in vivo[11,19,20,22,23,28–31], suggestive of a presynaptic hyperpolarization and/or increase in membrane conductance[15,34]. Consistent with these observations, intracellular recordings from monoamine cell bodies, which possess autoreceptors that are pharmacologically similar or identical to those at the terminals, reveal that autoreceptor stimulation leads to somadendritic hyperpolarization[1,2,9,36].

Although the ion(s) responsible for autoreceptor-mediated hyperpolarization in dopaminergic cell bodies has not yet been identified, in noradrenergic and serotonergic neurons, autoreceptor-mediated hyperpolarizations are due to a specific increase in conductance to potassium[1,2,36]. The nature of this potassium conductance change, and its susceptibility to blockade by pharmacological agents, are unknown, but a hyperpolarization mediated by an increase in potassium conductance at the nerve terminal could account for decreased terminal excitability and decreased transmitter release following terminal autoreceptor stimulation in monoamine neurons, similar to its effects in *Aplysia*[24]. Several distinct classes of voltage-sensitive potassium channels have been dem-

Correspondence: J.M. Tepper, Department of Psychiatry (M-003), School of Medicine, University of California, San Diego, La Jolla, CA 92093, U.S.A.

onstrated in various neurons, which can be blocked by the external application of the drugs 4-AP or TEA[3,32,33], and in *Aplysia*, 4-AP blocks the presynaptic modulation of transmitter release[24].

The present experiments were carried out in an attempt to elucidate the ionic mechanisms underlying dopamine autoreceptor-mediated decreases in terminal excitability. Striatal dopamine terminals are subject to endogenous autoinhibition in situ from dopamine released as a consequence of ongoing neuronal activity, as indicated by increases in terminal excitability subsequent to administration of dopamine autoreceptor antagonists or coincident with decreases in neuronal firing rate[29,30]. If terminal autoreceptors regulate the level of polarization and excitability of dopamine terminals through 4-AP- or TEA-sensitive potassium channels, then application of these potassium channel blockers would be expected to block endogenous terminal autoinhibition, thereby leading to increased dopaminergic terminal excitability, similar to the effects of dopamine antagonists[11,29,30].

MATERIALS AND METHODS

Subjects

Male Sprague–Dawley rats, housed 2 or 3 to a cage, weighing between 230 and 350 g at the time of recording, were the subjects for all experiments. Animals were anesthetized with 1.3 g/kg urethane (ethyl carbamate), i.p., and in some cases, the left femoral vein was cannulated for i.v. drug administration. Further details on animal preparation were as described previously[29].

Electrical stimulation and drug infusions

Stimulating electrodes consisted of bipolar stainless-steel enamel-coated wires, approximately 200 μm in diameter, with a tip separation of approximately 100 μm. Electrical stimuli to the ipsilateral dorsal anterior neostriatum (0.5 to −0.5 mm anterior to bregma, 3.5 mm lateral to the midline, 3.5 to 4.0 mm ventral to the cortical surface) consisted of single monophasic square-wave pulses of durations ranging from 10 to 500 μs at 0.3–3.0 mA, delivered at a rate of 1/s. Stimulating electrodes were individually calibrated in situ prior to each experiment, and were monitored periodically throughout all experiments to control for possible changes in impedance. A 32-gauge infusion cannula was connected by a short length of Teflon tubing to a 10 μl Hamilton microsyringe, controlled by a Harvard Apparatus infusion pump. The infusion cannula and the stimulating electrode were held in place with a small Narishige micromanipulator, and aligned so that the open end of the cannula was within 200 μm of the exposed tips of the stimulating electrode. Infusions consisted of a volume of 0.31 μl, delivered over the course of 5 min. In some cases, drugs were infused into, and excitability tested from preterminal regions of nigrostriatal axons in the medial forebrain bundle (MFB, 4.2 mm anterior to lambda, 1.75 mm lateral to the midline, 7.8 mm ventral to the cortical surface).

Drugs

The drugs used in these experiments were as follows: 4-aminopyridine (Sigma), 0.1 or 1.0 mM; tetraethylammonium chloride (Sigma), 100 mM; apomorphine (Sigma), 10 μM; and, for i.v. administration, haloperidol lactate (McNeil), 0.05–0.10 mg/kg. All drugs were dissolved in 0.9% saline, except for apomorphine which was prepared in 0.9% saline in 0.1% ascorbate. In some cases, rats were pretreated with alpha-methyl-*p*-tyrosine (AMpT; Sigma, 250 mg/kg, i.p.) 18 and 3–6 h prior to excitability testing in order to deplete endogenous levels of dopamine[17].

Recordings

Extracellular single unit recordings of electrophysiologically identified dopaminergic neurons[5,9,12,29,37] in substantia nigra pars compacta (2.1 mm anterior to lambda, 2.0 mm lateral to the midline, 6.8 to 7.5 mm from the dorsal surface of the brain) were obtained with glass micropipettes, filled with 3 M NaCl and possessing in vitro impedances of 4–10 MΩ at 500 Hz. Upon encountering dopaminergic neurons, the stimulus current and/or duration were varied in order to determine if the cell could be driven antidromically. Responses were considered to be antidromic provided that they collided with appropriately timed spontaneous discharges[7]. In addition, antidromic responses of dopaminergic neurons were characterized by their slow conduction velocity, constant latencies, and usually consisted of the initial segment spike only, as described previously[5,9,12,29]. Data were recorded on magnetic tape for off-line analysis.

Terminal excitability measurement

After antidromic activation was obtained, the stimulus current was reduced to the minimum value sufficient to elicit an antidromic response to every stimulus, termed the 'threshold' current. In practice, currents yielding 95% or more antidromic responses were considered to be at threshold. Thresholds were determined in a counterbalanced fashion from ascending and descending series of current increments and decrements, with steps approximately equal to 10% of the threshold value. In addition to the threshold, currents that evoked lower proportions of antidromic responding were also determined. At least 25–50 stimulus presentations were made at each current setting. After a stable baseline measure of terminal excitability was obtained, drugs were locally infused into the stimulation site. At the end of the infusion, the threshold and intermediate points were redetermined. In order to eliminate residual drug effects, only one cell was tested on each side of the brain, and the effects of systemic haloperidol administration were tested on only one cell per animal. Changes in threshold current were classified as increases, decreases, or no change (change in threshold of less than 5%). Significance tests of percent change in threshold current were performed using Student's *t*-test on log-transformed data in order to achieve additivity and homogeneity of variance.

RESULTS

Effects of 4-AP on dopaminergic terminal excitability

The results of all excitability experiments are summarized in Table I. 4-AP (100 μM or 1 mM) was infused into the neostriatal site of antidromic impulse initiation in 18 cases. Although the higher dose of 4-AP led to slightly larger increases in threshold than the lower dose, the difference was not statistically different, and the data were pooled. Neostriatal infusion of 4-AP led to a significant increase in threshold current ($t = 7.03$, df = 17, $P < 0.01$). Following 4-AP infusion, threshold increased in 15 cases (+28.8 ± 5.3%, mean ± S.E.M.), decreased in 1 case (−7%), and was unchanged in the remaining 2 cases (+2.0 ± 2.0%). The latency to the onset of decreased excitability following infusion of 4-AP was usually 4–6 min from the start of the infusion. A typical response to local infusion of 4-AP is illustrated for one neuron in Fig. 1. Each trace consists of the superimposition of 5 single sweeps. Responses to neostriatal stimulation at 1.00 mA, the predrug threshold, are shown in Fig. 1A. Antidromic responses are elicited to each stimulus. Following infusion of 100 μM 4-AP, even increasing the stimulus current to 1.07 mA does not elicit reliable antidromic responding (Fig. 1B), and it is necessary to increase the stimulus current to 1.29 mA in order to re-establish 100% antidromic re-

TABLE I

Effects of potassium channel blockers on dopaminergic terminal excitability

Excitability was tested from the site of drug infusion in all cases. Changes in the current required to elicit antidromic responses on 100% of the stimulus deliveries were classified as increase, decrease, or no effect (change in threshold current of less than 5%). The numbers within parentheses for each entry represent the mean ± S.E.M. change in threshold current for all cells falling within that category.

Condition	*Drug*	*n*	*Change in antidromic threshold current*		
			Increase	*Decrease*	*No change*
Neostriatal infusion	4-AP (0.1–1.0 mM)	18	15 (+28.8±5.3%)	1 (−7.0%)	2 (+2.0±2.0%)
MFB infusion	4-AP (0.1 mM)	5	1 (+10%)	0 –	4 (−0.5±2.0%)
Neostriatal infusion	TEA (0.1 mM)	5	5 (+27.2±6.5%)	0 –	0 –
Neostriatal infusion AMpT pretreatment	4-AP (0.1 mM)	6	2 (+7.5±1.5%)	2 (−11.5±5.5%)	2 (0±0)
Neostriatal infusion AMpT pretreatment	4-AP (0.1 mM) + APO (10 μM)	6	4 (+44.0±19.3%)	0 –	2 (1.5±1.5%)

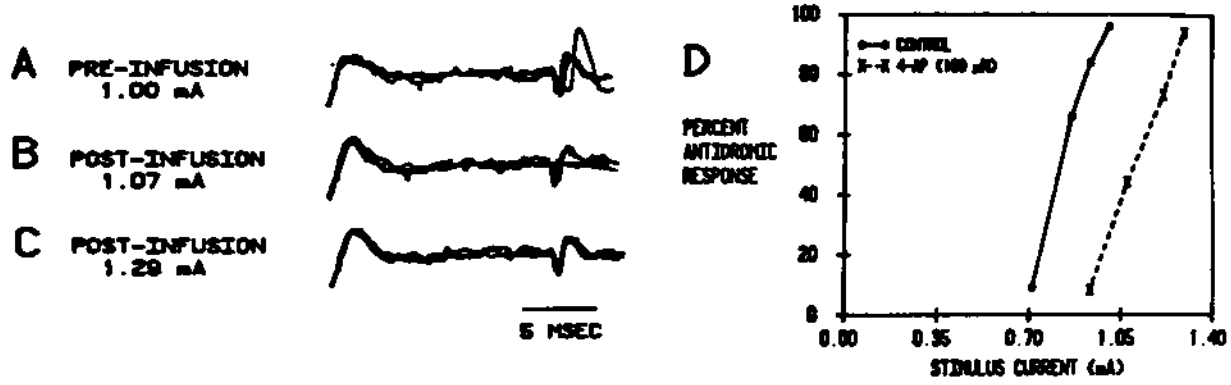

Fig. 1. Effect of neostriatal 4-AP infusion on dopaminergic terminal excitability. A–C: each trace consists of the superimposition of 5 consecutive single sweeps. In this, and all succeeding figures, stimuli were presented once per second. All traces are shown with positivity downwards. A: predrug threshold current (1.00 mA) elicits an antidromic response to every neostriatal stimulus. Note that most antidromic responses consist of the initial segment spike (IS) only, with full, initial segment-somadendritic antidromic (IS-SD) spikes occurring much less frequently. B: after local infusion of 4-AP (100 μM, 0.31 μl) into the neostriatal stimulating site, even increasing the stimulus current to 1.07 mA only elicited antidromic responses to 44% of the stimulus presentations, indicating decreased excitability. C: increasing stimulus current to 1.29 mA restored 100% antidromic responding. D: the solid line denotes the predrug current–response relation for this neuron. After 4-AP infusion, the entire curve is shifted in a parallel fashion to the right, indicating decreased excitability over the entire range of stimulating currents (broken line).

sponding (Fig. 1C). Fig. 1D summarizes the effects of 4-AP on this neuron. The pre-infusion excitability curve is shown by the solid line. Following 4-AP infusion, the curve is shifted in a parallel fashion to the right, indicating that increased stimulating currents are necessary to elicit equivalent proportions of antidromic responding at all currents compared to the pre-infusion control. We have previously shown that local infusion of vehicle into the terminal fields of monoamine neurons does not modify terminal excitability[19,23,29].

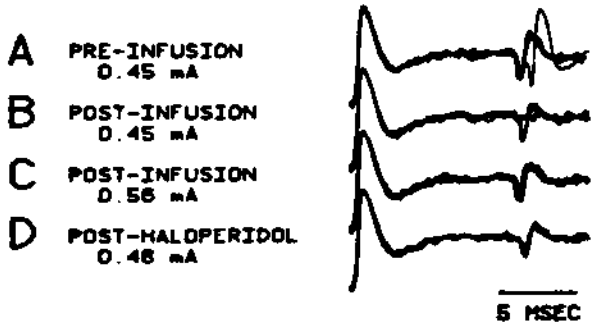

Fig. 2. Reversal of 4-AP induced decrease in terminal excitability by haloperidol. A: predrug threshold current (0.45 mA) evokes 100% antidromic responding. B: local infusion of 4-AP decreased excitability, and the same stimulus current only elicited 55% antidromic responding. Note the slight increase in antidromic latency. C: increasing stimulus current to 0.56 mA was necessary to re-establish 100% response rate. Note the increased latency variability. D: following i.v. administration of haloperidol (0.1 mg/kg), the decreased excitability was almost completely reversed, and the threshold current was reduced to 0.48 mA. Note that the antidromic latency variability is reduced (compare C to D).

Decreases in the excitability of terminal fields following neostriatal infusions of 4-AP were subject to reversal upon subsequent administration of the dopamine autoreceptor antagonist, haloperidol (n = 5), as shown in Fig. 2. Prior to drug infusion, threshold for 100% antidromic responding was 0.45 mA (Fig. 2A). Following infusion of 100 μM 4-AP, the excitability decreased and 0.45 mA elicited only 55% antidromic responding (Fig. 2B), and the threshold increased to 0.56 mA (Fig. 2C). The antidromic latency variability was also increased, as previously reported following autoreceptor-mediated decreases in dopaminergic terminal excitability[29]. Subsequent i.v. administration of 0.1 mg/kg haloperidol reversed the decrease in excitability, as indicated by the reduction in threshold current to 0.48 mA, and the reduced latency variability (Fig. 2D). In two additional cases, the effects of 4-AP on terminal excitability were prevented by preadministration of haloperidol (0.1 mg/kg, i.v.).

In order to examine whether the effects of 4-AP on excitability were specific to the terminal regions of these axons, 4-AP was infused into, and excitability tested from, preterminal regions of the axons in the

MFB in 5 animals. In marked contrast to the effects of neostriatal infusions of 4-AP on terminal excitability, infusion of 4-AP into the MFB did not alter excitability when measured from this site ($t = 1.37$, df = 4, $P = 0.24$). Infusion of 4-AP into the MFB elicited a small increase in threshold in one case (+7%) and had no effect in the remaining 4 cases (+1.25 ± 1.75) when tested from these more proximal regions of the axon, as summarized in Table I.

Effects of TEA on dopaminergic terminal excitability

Since pharmacologically and kinetically distinct types of potassium channels are known to exist, and display differential sensitivities to 4-AP[33], the effects of a second potassium channel blocker, TEA, were examined in 5 additional animals. The results were similar to those following 4-AP infusion. Following neostriatal infusion of 100 mM TEA, threshold increased in all 5 cases (+27.2 ± 6.5%; $t = 10.55$, df = 4, $P < 0.01$). A typical response to TEA infusion is shown in Fig. 3. Prior to infusion, the threshold stimulus current was 0.51 mA. Following TEA infusion, it was necessary to increase the stimulus current to 0.68 mA in order to re-establish 100% responding. Similar changes in antidromic response probability occurred at all stimulus currents, as shown by the dashed line in Fig. 3. Although attempted in only one case, the decreased terminal excitability caused by TEA infusion was reversed upon subsequent administration of haloperidol (0.05 mg/kg, i.v.), as shown in Fig. 3.

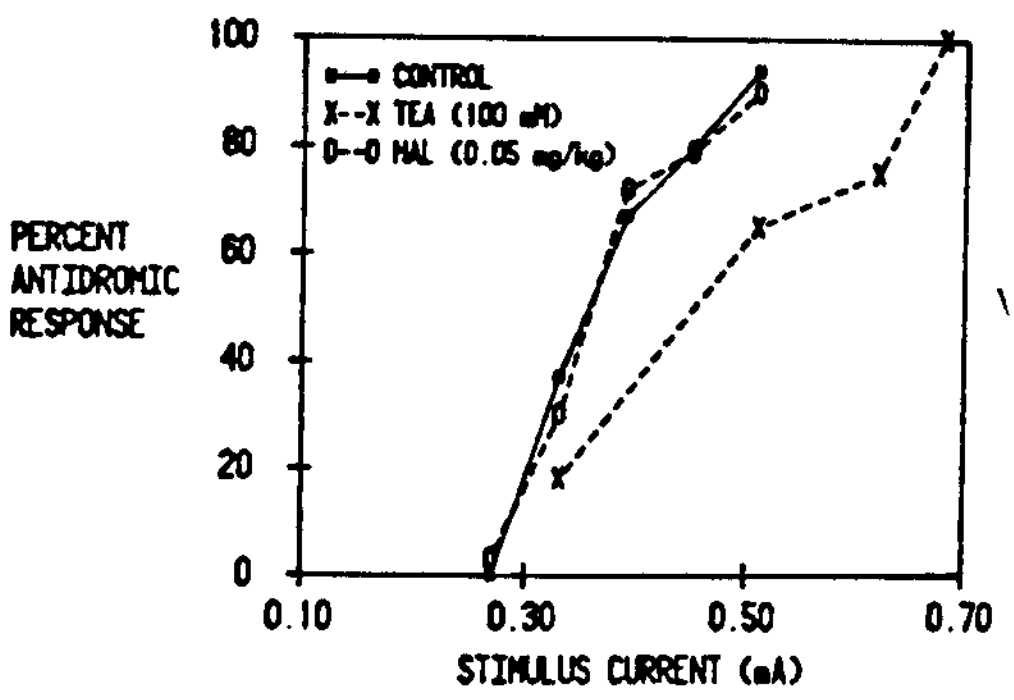

Fig. 3. Effects of TEA infusion on dopaminergic terminal excitability. The predrug current–response relation is indicated by the solid line. Following neostriatal infusion of TEA (100 mM), the curve is shifted in nearly uniform fashion to the right, indicating decreased terminal excitability (×--×). Subsequent i.v. administration of haloperidol (0.05 mg/kg) completely reversed the effects of the TEA infusion and returned the current–response relation to the predrug state (O--O).

Effects of dopamine depletion on responses to 4-AP

Since the decreased terminal excitability following 4-AP and TEA closely resembled effects seen following stimulation of the terminal autoreceptor by direct or indirect dopamine agonists[11,28,29], and since 4-AP and TEA have been shown to enhance transmitter release at other synapses[3,25,32], it appeared possible that the decreased terminal excitability induced by these potassium channel blockers was secondary to increased autoreceptor stimulation resulting from enhanced dopamine release. This suggestion was supported by the ability of haloperidol to antagonize 4-AP- and TEA-induced decreases in terminal excitability, and by the lack of effect of 4-AP at preterminal regions of the axon in the MFB, as described above. To test this hypothesis further, a separate group of rats was pretreated with AMpT (250 mg/kg i.p.), 18 and 3–6 h, prior to recording, in order to deplete endogenous stores of dopamine[17]. We have previously shown that this procedure abolishes the ability of amphetamine, which promotes the release and blocks the re-uptake of dopamine[16], to alter dopaminergic terminal excitability[29]. Infusion of 100 μM 4-AP into the neostriatum in AMpT-treated rats did not significantly alter terminal excitability ($t = -0.13$, df = 5, $P = 0.90$); in these animals 4-AP infusion led to a small threshold increase in two cases (+7.5 ± 1.5%), decreased threshold in two cases (−11.5 ± 5.5%), and was without effect in the remaining two cases (0.0 ± 0.0%), as summarized in Table I.

Effects of 4-AP on terminal excitability changes induced by apomorphine

Administration of exogenous dopamine autoreceptor agonists reduces the excitability of dopaminergic nigrostriatal axon terminals[29]. The ability of 4-AP to block apomorphine-induced decreases in terminal excitability was examined in 6 additional rats that were pretreated with AMpT as described above. Alpha-methyl-*p*-tyrosine pretreatment was necessary in order to prevent changes in terminal excitability resulting from the administration of 4-AP itself. Co-infusion of 10 μM apomorphine (APO) in a 100 μM 4-AP solution increased threshold for 4 neu-

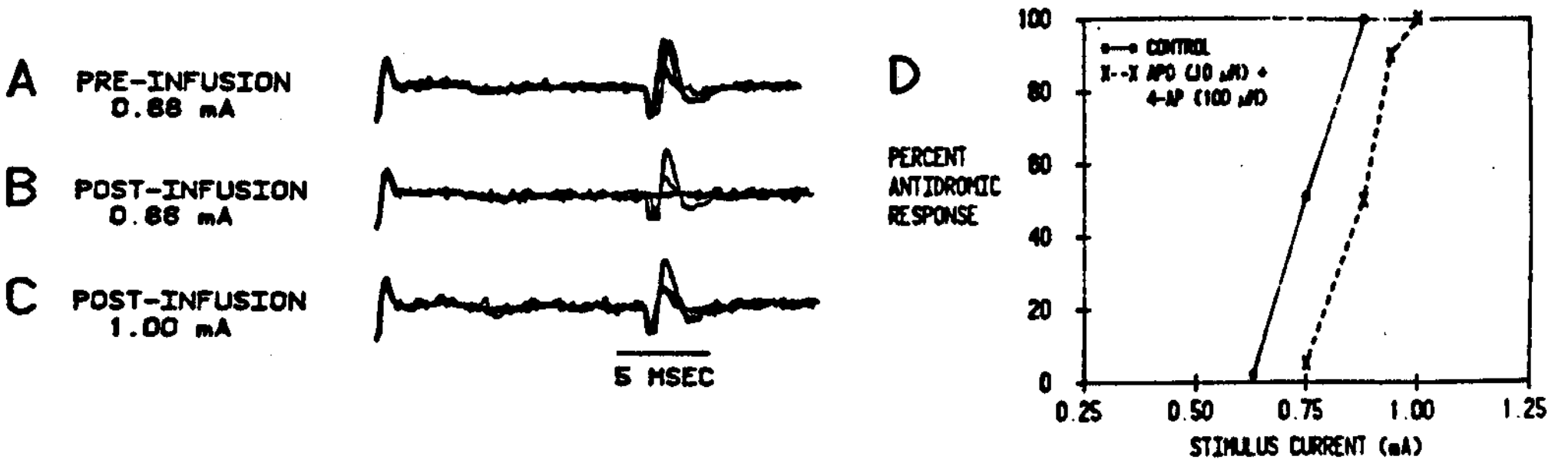

Fig. 4. Apomorphine-induced decreases in terminal excitability occur in the presence of 4-AP. The rat was pretreated with AMpT (250 mg/kg. i.p.) 18 and 4 h prior to recording. A: prior to 4-AP/APO infusion, 0.88 mA was at threshold and elicited antidromic responses to each stimulus. B: following co-infusion of apomorphine (10 μM) and 4-AP (100 μM), 0.88 mA elicited antidromic responses to only 50% of the stimuli. C: postdrug threshold responding at 1.00 mA. D: pre-drug current–response relation for this neuron is indicated by the solid line. Following infusion of 10 μM apomorphine in 100 μM 4-AP, terminal excitability decreased uniformly at all stimulus current levels, resulting in a parallel shift to the right in the current–response curve.

rons (+44.0 ± 19.3%), and had no effect on the remaining 2 cells (+1.5 ± 1.5%). This represents a significant decrease in terminal excitability from the predrug control (t = 3.56, df = 5, $P < 0.05$), and does not differ from the effects of apomorphine alone that we have reported previously[29]. Fig. 4A shows the antidromic responses of a dopaminergic neuron to threshold neostriatal stimulation (0.88 mA) before co-infusion of apomorphine and 4-AP. Following the infusion, this current becomes insufficient to elicit antidromic responses to each stimulus delivery (Fig. 4B). The post-drug threshold is increased to 1.0 mA (Fig. 4C). The decrease in excitability is evident at all current intensities, as illustrated for this neuron in Fig. 4D.

DISCUSSION

We have previously demonstrated that autoreceptor-mediated decreases in stimulated release of monoamines[4,6,8,13,26] occur under conditions of decreased terminal excitability, probably as a consequence of a terminal hyperpolarization and/or an increase in conductance[11,19–23,28–31]. If changes in the conductance of 4-AP- or TEA-sensitive potassium channels participate in the decreased terminal excitability resulting from dopaminergic autoreceptor stimulation, then application of 4-AP or TEA alone would be expected to increase dopaminergic terminal excitability, as do autoreceptor antagonists[11,29,30], since striatal dopamine terminals are subject to endogenous autoinhibition in vitro[26] and in vivo[29–31]. Similarly, the potassium channel blockers would be expected to prevent decreases in terminal excitability resulting from administration of exogenous autoreceptor agonists. However, local infusion of 4-AP and TEA led to consistent decreases in dopamine terminal excitability, and thus did not block endogenous autoinhibition at these terminals. Furthermore, 4-AP did not interfere with the ability of apomorphine to decrease terminal excitability. Thus, it is unlikely that changes in the conductance of 4-AP- or TEA-sensitive potassium channels underlie the decreases in terminal excitability seen following terminal autoreceptor stimulation in dopaminergic neurons. However, it must be noted that the present data do not rule out a role for increased potassium conductance in autoreceptor-mediated terminal hyperpolarizations, since it is possible that dopamine autoreceptor-activated potassium channels might not be sensitive to the effects of 4-AP or TEA.

It is also possible that dopaminergic neurons may differ from other monoaminergic neurons with respect to the ionic bases of the hyperpolarization resulting from autoreceptor stimulation. In noradrenergic and serotonergic neurons, the autoreceptor-mediated hyperpolarization of the soma-dendrite is due to a specific increase in conductance to potassium[1,2,36], although the sensitivity of this potassium conductance to blockade by 4-AP or TEA has not been determined electrophysiologically. In contrast to these effects, the sole intracellular study of autore-

ceptor effects at the dopamine cell body reported that the hyperpolarization resulting from i.v. apomorphine is accompanied by a negligible increase in input impedance[10]. This latter study was performed in vivo, thus precluding the possibility of altering the ionic composition of the extracellular fluid in order to determine with any certainty the underlying cause of the hyperpolarization. In further support of the suggestion that there may exist a different ionic basis for autoreceptor-mediated hyperpolarizations in dopaminergic versus noradrenergic and serotonergic neurons, a recent in vitro voltage clamp study of conductance changes elicited by dopamine agonists in artificial lipid bilayers containing functionally reconstituted dopamine receptors obtained from crude striatal homogenates indicates that the striatal D2 dopamine receptor may act to increase conductance to chloride[18]. Since the dopamine autoreceptor has been functionally identified as a D2 dopamine receptor[27], these results might explain the lack of ability of 4-AP and TEA to block terminal autoinhibition in the present study.

However, although neither 4-AP nor TEA directly affected the response to endogenous or exogenously applied dopamine autoreceptor agonists, both potassium channel-blockers led to marked decreases in dopamine terminal excitability, which could be reversed or blocked by systemic administration of the dopamine receptor antagonist, haloperidol. This finding suggested that the decreased terminal excitability induced by the potassium channel blockers resulted from increased stimulation of autoreceptors at the terminal, perhaps as a consequence of enhanced dopamine release, a hypothesis consistent with the known abilities of 4-AP and TEA to increase transmitter release at several other, neurochemically distinct, terminals[3,14,25,32,35]. In order to assess this possibility, the effects of 4-AP on terminal excitability were examined in rats depleted of endogenous dopamine by pretreatment with AMpT. In pretreated rats, 4-AP failed to modify terminal excitability, indicating that the phenomenon required the presence of endogenous dopamine. Consistent with these observations, the local infusion of 4-AP into preterminal regions of dopamine axons in the MFB did not change the excitability of these more proximal regions of the axon. We have previously shown that, in contrast to neostriatal terminal fields, the excitability of preterminal axons in the medial forebrain bundle are not subject to modulation by autoreceptor agonists or antagonists, suggesting that autoreceptors are not present along the preterminal, presumably nonsynaptic, regions of nigrostriatal dopaminergic axons[11,28-30]. These results indicate that the effects of the potassium channel blockers on dopamine terminal excitability are indirect, and result from increased autoreceptor stimulation as a consequence of enhanced release of endogenous dopamine, which in turn leads to increased activation of terminal autoreceptors and a reduction in terminal excitability.

In summary, our results indicate that transmitter release from dopaminergic neurons can be enhanced by 4-AP and TEA, as indicated by the decrease in terminal excitability following infusion of these drugs into dopaminergic terminal fields. Whether the increased transmitter release is due to a blockade of potassium channels or a direct action on calcium channels remains to be clarified. Furthermore, the fact that 4-AP and TEA failed to interfere with endogenous autoinhibition at the terminals, as well as the inability of 4-AP to block apomorphine-induced decreases in terminal excitability in dopamine-depleted animals, argues against a role of 4-AP- and TEA-sensitive potassium channels in the mediation of autoinhibitory processes at the terminals of dopaminergic nigrostriatal axons.

ACKNOWLEDGEMENTS

This research was supported by Grant DA 02854 and Research Scientist Award DA 00079 (to P.M.G.) from the National Institute on Drug Abuse.

REFERENCES

1 Aghajanian, G.K. and Lakoski, J.M., Hyperpolarization of serotonergic neurons by serotonin and LSD: studies in brain slices showing increased K^+ conductance, *Brain Research*, 305 (1984) 181–185.

2 Aghajanian, G.K. and VanderMaelen, C.P., Alpha$_2$ adrenoceptor-mediated hyperpolarization of locus coeruleus neurons: intracellular studies in vivo, *Science*, 215 (1982) 1394–1396.

3 Bowman, W.C. and Savage, A.O., Pharmacological actions of aminopyridines and related compounds, *Rev. Pure*

Appl. Pharmacol. Sci., 2 (1981) 317–371.
4 Chesselet, M.-F., Presynaptic regulation of neurotransmitter release in the brain: facts and hypotheses, *Neuroscience*, 12 (1984) 347–375.
5 Deniau, J.M., Hammond, C., Rizk, A. and Feger, J., Electrophysiological properties of identified output neurons of the rat substantia nigra (pars compacta and pars reticulata): evidence for the existence of branched pathways, *Exp. Brain Res.*, 32 (1978) 409–422.
6 Farnebo, L.-O. and Hamberger, B., Drug-induced changes in the release of ^{3}H-monoamines from field stimulated rat brain slices, *Acta Physiol. Scand.*, (Suppl.), 371 (1971) 35–44.
7 Fuller, J.H. and Schlag, J.D., Determination of antidromic excitation by the collision test: problems of interpretation, *Brain Research*, 112 (1976) 238–298.
8 Göthert, M., Serotonin-receptor-mediated modulation of Ca^{2+}-dependent 5-hydroxytryptamine release from neurones of the rat brain cortex, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 314 (1980) 223–230.
9 Grace, A.A. and Bunney, B.S., Intracellular and extracellular electrophysiology of nigral dopaminergic neurons—1. Identification and characterization, *Neuroscience*, 10 (1983) 301–315.
10 Grace, A.A. and Bunney, B.S., Low doses of apomorphine elicit two opposing influences on dopamine cell electrophysiology, *Brain Research*, 333 (1985) 285–298.
11 Groves, P.M., Fenster, G.A., Tepper, J.M., Nakamura, S. and Young, S.J., Changes in dopaminergic terminal excitability induced by amphetamine and haloperidol, *Brain Research*, 221 (1981) 425–431.
12 Guyenet, P.G. and Aghajanian, G.K., Antidromic identification of dopaminergic and other output neurons of the rat substantia nigra, *Brain Research*, 150 (1978) 69–84.
13 Kamal, L.A., Arbilla, S. and Langer, S.Z., Presynaptic modulation of the release of dopamine from the rabbit caudate nucleus: differences between electrical stimulation, amphetamine and tyramine, *J. Pharmacol. Exp. Ther.*, 216 (1981) 592–598.
14 Kirpekar, S.M., Prat, J.C. and Schiavone, M.T., Modification of potassium-evoked release of noradrenaline by various ions and agents, *Br. J. Pharmacol.*, 78 (1983) 227–235.
15 Kocsis, J.D. and Waxman, S.G., Intra-axonal recordings in rat dorsal column axons: membrane hyperpolarization and decreased excitability precede the primary afferent depolarization, *Brain Research*, 238 (1982) 222–227.
16 Kuczenski, R., Biochemical actions of amphetamine and other stimulants. In I. Creese (Ed.), *Stimulants: Neurochemical, Behavioral, and Clinical Perspectives*, Raven Press, New York, 1983, pp. 31–61.
17 Moore, K.E. and Dominic, J.A., Tyrosine hydroxylase inhibitors, *Fed. Proc. Fed. Am. Soc. Exp. Biol.*, 30 (1971) 859–870.
18 Murphy, R.B. and Vodyanoy, V., Functional reconstitution of rat striatal dopamine agonist receptors into artificial lipid bimolecular membranes, *Biophys. J.*, 45 (1984) 22–23.
19 Nakamura, S., Tepper, J.M., Young, S.J. and Groves, P.M., Neurophysiological consequences of presynaptic receptor activation: changes in noradrenergic terminal excitability, *Brain Research*, 226 (1981) 155–170.
20 Nakamura, S., Tepper, J.M., Young, S.J. and Groves, P.M., Changes in noradrenergic terminal excitability induced by amphetamine and their relation to impulse traffic, *Neuroscience*, 7 (1982) 2217–2224.
21 Ryan, L.J., Tepper, J.M., Young, S.J. and Groves, P.M., Amphetamine's effects on terminal excitability of noradrenergic locus coeruleus neurons are impulse-dependent at low but not high doses, *Brain Research*, 341 (1985) 155–163.
22 Ryan, L.J., Tepper, J.M., Sawyer, S.F., Young, S.J. and Groves, P.M., Autoreceptor activation in central monoamine neurons: modulation of neurotransmitter release is not mediated by intermittent axonal conduction, *Neuroscience*, 15 (1985) 925–931.
23 Sawyer, S.F., Tepper, J.M., Young, S.J. and Groves, P.M., Antidromic activation of dorsal raphe neurons from neostriatum: physiological characterization and effects of terminal autoreceptor activation, *Brain Research*, 332 (1985) 15–28.
24 Shimahara, T., Presynaptic modulation of transmitter release by the early outward potassium current in *Aplysia*, *Brain Research*, 263 (1983) 51–56.
25 Stanfield, P.R., Tetraethylammonium ions and the potassium permeability of excitable cells, *Rev. Physiol. Biochem. Pharmacol.*, 97 (1983) 1–67.
26 Starke, K., Presynaptic autoreceptors. In H. Yoshida, Y. Hagiwara and S. Ebashi (Eds.), *Advances in Pharmacology and Therapeutics III, Vol. 2, Neurotransmitter Receptors*, Pergammon Press, Japan, 1981, pp. 131–139.
27 Starke, K., Spath, L., Lang, J.D. and Adelung, C., Further functional in vitro comparison of pre- and postsynaptic dopamine receptors in the rabbit caudate nucleus, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 323 (1983) 298–306.
28 Takeuchi, H., Young, S.J. and Groves, P.M., Dopaminergic terminal excitability following arrival of the nerve impulse: the influence of amphetamine and haloperidol, *Brain Research*, 245 (1982) 47–56.
29 Tepper, J.M., Nakamura, S., Young, S.J. and Groves, P.M., Autoreceptor-mediated changes in dopaminergic terminal excitability: effects of striatal drug infusions, *Brain Research*, 309 (1984) 317–333.
30 Tepper, J.M., Young, S.J. and Groves, P.M., Autoreceptor-mediated changes in dopaminergic terminal excitability: effects of increases in impulse flow, *Brain Research*, 309 (1984) 309–316.
31 Tepper, J.M., Groves, P.M. and Young, S.J., The neuropharmacology of the autoinhibition of monoamine release, *Trends Pharmacol. Sci.*, 6 (1985) 251–255.
32 Thesleff, S., Aminopyridines and synaptic transmission, *Neuroscience*, 5 (1980) 1413–1419.
33 Thompson, S.H., Three pharmacologically distinct potassium channels in molluscan neurones, *J. Physiol. (London)*, 265 (1977) 465–488.
34 Wall, P.D., Excitability changes in afferent fibre terminations and their relation to slow potentials, *J. Physiol. (London)*, 142 (1958) 1–21.
35 Wemer, J., Scheffelmeer, N.M. and Mulder, A.H., Studies on the role of Na^+, K^+, and Cl^- ion permeabilities in K^+-induced release of ^{3}H-noradrenaline from rat brain slices and synaptosomes and in its presynaptic α-adrenergic modulation, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 317 (1981) 103–109.
36 Williams, J.T., Henderson, G. and North, R.A., Characterization of alpha$_2$ adrenoceptors which increase potassium conductance in rat locus coeruleus neurons, *Neuroscience*, 14 (1985) 95–101.
37 Wilson, C.J., Young, S.J. and Groves, P.M., Statistical properties of neuronal spike trains in the substantia nigra: cell types and their interactions, *Brain Research*, 136 (1977) 243–260.