Dopamine Enhances Terminal Excitability of Hippocampal–Accumbens Neurons via D2 Receptor: Role of Dopamine in Presynaptic Inhibition

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The effects of dopamine on the axonal terminals of hippocampal–nucleus accumbens (HIPP-ACC) neurons were investigated in urethane-anesthetized rats using extracellular single-unit recording techniques. Antidromic responses recorded in the ventral subiculum of the hippocampus were evoked by stimulation of the medial accumbens. Baseline terminal excitability of these neurons, established by threshold stimulation of the accumbens, was markedly enhanced by conditioning stimulation (10 Hz) of the ventral tegmental area (VTA), the origin of the mesolimbic dopaminergic neurons. Iontophoretic application of sulpiride, a selective D2 antagonist, onto the HIPP-ACC terminals attenuated the increased terminal excitability of these neurons produced by conditioning VTA stimulation, while intraperitoneal injection of SCH23390, a selective D1 antagonist, failed to attenuate this effect. Iontophoretic application of dopamine or its selective D2 agonist, LY171555, onto the terminals of the HIPP-ACC neurons mimicked the prolonged enhancement of the terminal excitability produced by VTA stimulation, whereas SKF38393, a D1 agonist, had no effect. The effects of VTA stimulation, dopamine and LY171555 application were similar after the accumbens had been pretreated with ibotenic acid, suggesting a direct action of dopamine on the axonal terminals of HIPP-ACC neurons, and that changes in terminal excitability were not mediated via interneurons or feedback pathways from the accumbens to the hippocampus. Since iontophoretic application of potassium, a depolarizing agent, also enhanced the terminal excitability of the HIPP-ACC neurons, it appears that dopamine depolarized, via D2 receptors, the axonal terminals of HIPP-ACC neurons. Moderate terminal depolarization below threshold for action potentials appears to lower the threshold and increase the excitability of the neurons and may consequently reduce the quantal release of excitatory transmitter from the HIPP-ACC terminals. This mechanism of presynaptic inhibition may constitute part of a “gating” action of dopamine in regulating limbic afferent inputs in the nucleus accumbens.

The mesolimbic dopaminergic (DA) pathway, which originates from the ventral tegmental area (VTA) and terminates in the nucleus accumbens of the ventral striatum (Dahlstrom and Fuxe, 1964; Swanson, 1982), has a modulatory role in limbic–motor integration (Mogenson, 1984). Electrical stimulation of the VTA attenuates the excitatory inputs to the nucleus accumbens from

the amygdala (Yim and Mogenson, 1982) or from the hippocampus (Yang and Mogenson, 1984) with little or no effect on the basal firing rate of the accumbens neurons. The attenuation effect produced by VTA stimulation was blocked by dopamine antagonists and by 6-hydroxydopamine lesions of the VTA (Yang and Mogenson, 1984; Yim and Mogenson, 1982). These observations suggest that the attenuation was dopamine-mediated and led to the hypothesis that dopamine may exert a “gating” action on limbic afferent inputs to the nucleus accumbens (Mogenson, 1984; Stevens and Livermore, 1978). The gated limbic signals may subsequently be relayed from the nucleus accumbens to basal forebrain motor effector sites to initiate adaptive behaviors (Mogenson, 1984; Yang and Mogenson, 1985b).

The synaptic mechanisms by which dopamine influences excitatory limbic inputs to the accumbens are unclear. However, recent neurochemical studies have provided some clues to the synaptic actions of dopamine in the striatum. In rat striatal slices and synaptosomal preparations, potassium-depolarized release of preloaded triitated glutamate is blocked by dopamine or its agonists (Mitchell and Doggett, 1980; Rowland and Roberts, 1980). Removal of corticostriatal afferents by decortication reduces binding sites for the D2 type dopamine receptors in rat striatum (Schwarcz et al., 1978; Theodorou et al., 1981). It was observed, using a push–pull perfusion preparation in cats, that the release of preloaded labeled glutamate in striatum upon stimulation of the frontal cortex is inhibited by perfusing dopamine or its agonists to the striatum or by conditioning stimulation of the substantia nigra (Godukhin et al., 1984). These neurochemical studies suggested that dopamine regulates transmitter release from glutamatergic corticostriatal neurons via D2 receptors located on their striatal afferent terminals (Brown and Arbutnot, 1983), but the synaptic mechanisms by which dopamine acts on these terminals are unknown.

The present study employed an electrophysiological test of terminal excitability (Curtis and Ryall, 1966; Lisney, 1979; Wall, 1958; Willis et al., 1973) to investigate the actions of dopamine on the terminals of the antidromically identified hippocampal–accumbens (HIPP-ACC) neurons. With the availability of selective dopamine D1 and D2 receptor agonists and antagonists (Iorio et al., 1983; O'Connor and Brown, 1982; Setler et al., 1978; Stoof and Kebabian, 1984; Titus et al., 1983), microiontophoretic studies were also carried out to find out which dopamine receptor was mediating the modulatory effect on the HIPP-ACC axonal terminals.

Materials and Methods

Extracellular single-unit recordings, electrical stimulation, and iontophoresis

Experiments were carried out in urethane-anesthetized (1.0 g/kg) male Wistar rats (250–300 g) using standard extracellular single-unit recording techniques as described in detail previously (Yang and Mogenson,

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The possibility that dopamine, or its D2 agonists and antagonists, changes the terminal excitability indirectly via intrinsic accumbens interneurons or via pathways feeding back from the nucleus accumbens to the hippocampus was ruled out by injecting ibotenic acid, an axon-sparing neurotoxin, into the medial accumbens of 19 rats 7–9 d before each electrophysiological recording session (Kohler and Schwarcz, 1983; Yang and Mogenson, 1984). The unilateral accumbens injection of ibotenic acid was performed in rats under Nembutal anesthesia (60 mg/kg, i.p.). Ibotenic acid (3 μ g/0.5 μ l in PBS, pH 7.4) was injected through a 30 gauge stainless steel cannula connected to a Hamilton microliter syringe by a PE-10 polyethylene tubing (Clay Adamson, Parsippany, NJ) into the medial accumbens at a rate of 0.1 μ l/min. After the injection, the cannula was left in the accumbens for an additional 5 min to avoid backflow along the cannula track. The rats were returned to their home cage for 7–9 d with food and water available *ad libitum* before being used in electrophysiological recording experiments.

Figure 2. Antidromic responses of a HIPP-ACC neuron and the distribution of the onset latencies of these responses. *A*, Antidromic responses of a ventral subiculum neuron of the hippocampus to medial accumbens stimulation (50 μA , 0.2 msec, 0.6 Hz, 5 sweeps) that met the criteria of constant latency, all-or-nothing responses at threshold stimulation. The square pulse in the upper channel of the oscilloscope tracing indicates the pulse of the sampling time gate. The occurrence of the antidromic responses fell within the gated interval of the sampling time pulse. *B*, Another criterion was high-frequency following that was tested by paired-pulse suprathreshold stimulation. In this neuron, the delay interval of the 2 pulses was 2.6 msec. *C*, In the same neuron, antidromic responses followed up to 500 Hz since the second pulse failed to evoke an antidromic response when the delay interval between the 2 pulses was shortened to 2.1 msec (calibration: 2 msec, 100 μV). *D*, Histogram showing the onset latencies of the antidromic responses, with the majority of the responses occurring typically at 10–12 msec.

Histological verification of stimulation and recording sites

At the end of each experiment, stimulus sites were marked by an iron deposit by passing a 10 μA anodal current through the VTA-stimulating electrode for 1 min. For the accumbens-stimulating sites, pontamine sky blue was iontophoretically injected via one of the side barrels of the multibarrel pipette assembly with a cathodal current at 150 nA for 10 min. The animal was perfused transcardially first with saline and then by 3% solution of potassium ferricyanide in buffered formalin. A ferri-ferricyanide redox reaction produced a Prussian blue spot marking the VTA electrode site, while a blue dye deposit marked the accumbens stimulation site. The brain was subsequently removed and fixed in formalin for 24 hr. Frozen coronal sections from the appropriate regions were cut 70 μm thick with a Leitz freezing microtome and stained with Neutral Red for histological verification of the stimulation and recording sites under microscope.

Results

Antidromic responses of ventral subiculum neurons to medial accumbens stimulation and changes of their excitability by conditioning stimulation of the VTA

Single pulse stimulation (0.15–0.2 msec pulse width at 0.5 Hz) of the medial accumbens elicited short-latency antidromic action potentials in 283 hippocampal neurons studied. The onset latencies of 80% of them fell within the range of 10–12 msec, as shown by the single peak of the unimodal distribution of the onset latencies (Fig. 2D). Since all the antidromic responses exhibited a typical triphasic wave form with the duration of the action potential of at least 1 msec (Fig. 2, A–C), they are considered extracellular recordings from the cell bodies of HIPP-

Figure 3. Effects of conditioning VTA stimulation on the poststimulation firing index of HIPP-ACC neurons. Baseline firing index was monitored for 10 min before conditioning VTA stimulation (500 μA , 5 trains of 10 Hz pulses, $n = 21$) delivered at time shown by arrow. A 150% increase in firing index occurred during (filled circle; one-way ANOVA: $F(30,254) = 5.13$, $p < 0.001$), and persisted after, VTA stimulation. Recovery to baseline level occurred 8 min after termination of VTA stimulation. All values are expressed in mean $\pm$ SEM.

Table 1. Number of hippocampal neurons antidromically activated by accumbens stimulation and tested with conditioning VTA stimulation, or with iontophoretic application of DA, LY171555 or SKF38393 onto the terminal region of HIP-ACC neurons

Firing index	Number of antidromic responses tested with						Total tested
	Conditioning VTA stimulation (200–800 μ A)	Iontophoretic application of DA (40–160 nA)	Responded to both VTA stimulation and DA application	Iontophoretic application of LY171555	Responded to both DA and LY171555	Responded to LY171555, but not to SKF38393	
1. Enhanced ^a firing index	78/110 (71) ^b	36/70 (51)	12/33 (36)	33/69 (48)	6/17 (35)	21/35 (60)	212
No response	32/110 (29)	35/70 (49)	—	36/69 (52)	—	—	
2. Enhanced firing index after ibotenic acid lesion of accumbens	36/54 (67)	10/17 (59)	5/15 (33)	9/15 (60)	—	—	71
No response	18/54 (33)	7/17 (41)	—	6/15 (40)	—	—	

^a Only neurons which showed changes in firing index by 100% or more are included here (see Fig. 1 and Materials and Methods).

^b Numbers in parentheses = %.

ACC neurons. There was some fluctuation of the baseline firing index. Hence, during the control period, periodic fine adjustment of the accumbens stimulation by changing the pulse duration at 0.01 msec step up to a maximum of 0.25 msec was done to ensure a stable baseline firing index. Neurons that did not maintain a stable baseline firing index of 30–40 in a minimum of 6 consecutive sets, or whose firing index fluctuated more than 50% of the initial value, were excluded ($n = 35$).

Conditioning pulses (200–800 μ A, 5–10 trains, 10 pulses/train delivered at 0.6 Hz), but not single pulses, presented to the VTA, 40–80 msec before each single-pulse stimulation of the accumbens produced an abrupt increase in firing index that was twice the control values in 78 of 110 neurons tested (Fig. 3, Table 1). However, if the accumbens stimulation was adjusted so that the baseline firing index was near zero, conditioning VTA stimulation produced little or no change in this baseline firing index.

The enhancement of the firing index continued for several minutes (Fig. 3) and was of greater magnitude (Fig. 4) and of longer duration with higher intensity VTA stimulation (compare Fig. 6A, 200 μ A, with Fig. 6B, 400 μ A). In 21 neurons studied, recovery occurred in 8–10 min (Fig. 3) and for another 25 neurons, recovery did not occur during the recording period of up to 3 hr.

Iontophoretic application of dopamine to the axonal terminals of HIP-ACC neurons

The firing index of 36 of 70 (51%) HIP-ACC neurons was also enhanced by the iontophoretic application of dopamine (60–160 nA, for 30–90 sec) to their axonal terminals. For 12 of 33 (36%) of these neurons, there was an enhanced firing index with iontophoretically applied dopamine as well as with conditioning VTA stimulation (Fig. 5A). Although both VTA stimulation and dopamine application produced a similar increase in firing index, the onset of the dopamine effect was more gradual than that produced by conditioning VTA stimulation. Usually, the onset of the effects of iontophoretically applied dopamine took 30–100 sec to develop. In addition, iontophoretic application of potassium, a depolarizing agent, to the axonal terminals of 3 HIP-ACC neurons produced a similar increase in firing index. In cases for which no changes in firing index were observed following either VTA stimulation or dopamine application, it is likely that the accumbens stimulating electrode was positioned on the preterminal regions of HIP-ACC axons, where dopamine receptors are absent and, hence, the effects of dopamine receptor activation could not be detected.

Comparison of selective D1 and D2 antagonists on the enhanced firing index produced by conditioning VTA stimulation

The enhanced firing index from conditioning VTA stimulation was blocked by sulpiride, a dopamine D2 antagonist, when administered iontophoretically (20–80 nA, 9 of 11 neurons; Fig. 6A) or by intraperitoneal injection (20 mg/kg, 5 of 7 neurons). The sulpiride treatment blocked the enhanced firing index of the same neuronal terminals that were blocked by conditioning VTA stimulation or iontophoretic application of dopamine

Figure 4. Firing index of HIP-ACC neurons as the intensity of VTA stimulation was increased. Open bars, mean firing index of the last 5 consecutive sets of test trials (each firing index was tabulated from antidromic responses evoked from 20 presentations of accumbens stimulation that made up a set of test trials) prior to conditioning VTA stimulation; filled bars, mean firing index determined from 5 sets of poststimulation trials following conditioning VTA stimulation (10 trains of 10 Hz pulses delivered at 0.6 Hz/VTA train). Current intensity is indicated in the abscissa. Numbers at the bottom of each histogram indicate the number of neurons studied in each group. Asterisks indicate $p < 0.001$ (paired t test).

Figure 5. Effects of conditioning VTA stimulation, iontophoretic application of DA, its D1 agonist SKF38393, and its D2 agonist LY171555 on the firing index of 2 HIPP-ACC neurons. *A*, Conditioning VTA stimulation (200 μ A, 5 trains of 10 Hz pulses) elicited an increase in firing index that lasted for 14 min. Subsequent iontophoretic application of dopamine (50 nA) also produced a similar prolonged increase in the firing index of the same neuron. *B*, In another HIPP-ACC neuron, iontophoretic application of the D-1 agonist SKF38393 (60 nA) did not change the baseline firing index, whereas iontophoretic application of LY171555 (60 nA), a dopamine D2 agonist, produced a 4-fold increase in the firing index for more than 12 min.

(iontophoretic application of sulpiride: 2 of the 11 neurons studied; intraperitoneal injection of sulpiride: 3 of the 7 neurons studied). When the conditioning VTA stimulation (5 trains of 10 Hz pulses) was repeated at intervals of 200 sec the firing index returned to the predrug control level (Fig. 6A).

No change in the enhanced firing index was produced by conditioning VTA stimulation in any of the 7 neurons tested when SCH23390, a selective central dopamine D1 antagonist (6–10 mg/kg suspended in 0.4% methylcellulose; Iorio et al., 1983), was injected intraperitoneally (Fig. 6B).

Comparison of selective D1 and D2 agonists on firing index of HIPP-ACC neurons

In order to permit detection of increases or decreases of the firing index with the iontophoretic application of the D1 and D2 agonists, stimulating current delivered to the accumbens was first adjusted to produce a baseline firing index of 40–50. Direct iontophoretic application of LY171555, on quinpirole hydrochloride (60–160 nA), a selective dopamine D2 agonist, onto axonal terminals of HIPP-ACC neurons, enhanced the firing

Figure 6. Effects of iontophoretic application of sulpiride, a dopamine D2 antagonist, and intraperitoneal injection of SCH 23390, a dopamine D1 antagonist, on the increased firing index of HIPP-ACC neurons produced by conditioning VTA stimulation. *A*, Conditioning stimulation of VTA (200 μ A, 5 trains of 10 Hz pulses) produced a 4-fold increase in firing index of this neuron. Following recovery to baseline, the increase in firing index produced by the same VTA stimulation was blocked by iontophoretic application of sulpiride (80 nA). *B*, In another neuron, conditioning VTA stimulation (400 μ A, 5 trains of 10 Hz pulses) produced over a 2-fold increase in firing index during and after the stimulation. The enhanced firing index lasted for 800 sec. Intraperitoneal injection of SCH 23390 (6 mg/kg) did not block the enhanced firing index produced by conditioning VTA stimulation.

index in 17 of 31 cells (55%) tested (Fig. 5B); in 6 of 17 cells (35%), the firing index was increased by both the iontophoretic application of DA or LY171555. The onset of responses and the prolonged duration of the enhanced firing index produced by LY171555 or dopamine were similar. However, iontophoretic application of SKF38393, a dopamine D1 agonist, did not change the firing index over the current range of 40–120 nA. At higher iontophoretic current (140–160 nA), this D1 agonist had a tendency to suppress baseline firing index of the HIPP-ACC neurons. A differential response to SKF38393 (no change) and LY171555 (enhanced) was observed in 21 of 35 neurons (60%) tested (Fig. 5B). The percentage change in firing index is shown in Figure 7. The dopamine effect was greater than that produced

by LY171555, and this may reflect a lower starting baseline firing index used to obtain a better resolution in the responses for the dopamine effects, i.e., primarily an enhancement in firing index.

Effects of ibotenic acid lesions of the medial accumbens on the firing index produced by conditioning VTA stimulation, iontophoretic application of dopamine, or its D2 agonist, LY171555

Ibotenic acid lesions of the accumbens did not change the onset or duration of the enhanced firing index due to conditioning VTA stimulation in 36 of 54 neurons (67%) tested (Table 1). The enhanced firing index produced by the iontophoretic application of dopamine in 59% (10 of 17) or of LY171555 in 60% (9 of 15) of neurons was also unaffected. Five of 15 (33%) cells responded to both conditioning VTA stimulation and iontophoretic application of DA. The proportion of neurons showing an enhanced firing index by VTA stimulation or dopamine application was not significantly different from normal rats ($\chi^2 = 0.63$, $p > 0.1$). Histological examination of brain sections stained with thionine showed a loss of intrinsic accumbens neurons and extensive gliosis confined to the dorsal medial part of the nucleus accumbens.

Discussion

Stimulation of the medial part of the accumbens evoked antidromic responses from neurons recorded in the ventral subiculum of the hippocampus. The mean onset latencies of these responses were similar to the latencies of the orthodromic excitatory responses of accumbens neurons to stimulation of the ventral subiculum (Lopes da Silva et al., 1984; Yang and Mogenson, 1984). It appears likely that they are the glutamatergic neurons (Walaas, 1978; Walaas and Fonnum, 1979) that originate from the ventral subiculum and terminate in the medial accumbens (Kelley and Domesick, 1982; Yang and Mogenson, 1984).

The terminal excitability of HIPP-ACC neurons, as reflected by the firing index, was enhanced substantially when the VTA was stimulated by trains of conditioning pulses (10 Hz), but single pulses were ineffective. Trains of conditioning pulses to the VTA mimicked the characteristic burst firing pattern of dopaminergic neurons (Grace and Bunney, 1984; Yim and Mogenson, 1980). Such high-frequency stimulation of dopaminergic neurons was shown, in a recent study using *in vivo* voltammetry, to produce a larger striatal release of dopamine than from single-pulse stimulation (Gonon and Buda, 1985). If the accumbens stimulation current were adjusted to produce a baseline firing index near zero, conditioning stimulation of the VTA did not change the firing index. These observations suggest that dopamine did not tonically influence resting HIPP-ACC neurons but enhanced their terminal excitability when the glutamatergic synapse was activated, e.g., by a depolarizing current delivered to their terminals by the accumbens electrode (Godukhin et al., 1984; Nicoullon et al., 1983). Therefore, it appears that some background activity in the terminal of HIPP-ACC neurons is necessary for the subsequent action of dopamine.

Iontophoretic application of dopamine on the axonal terminals of HIPP-ACC neurons also enhanced the firing index of the same neurons, but the onset of response to the extrinsic application of dopamine was more gradual. It is possible that the abrupt enhancement of firing index of HIPP-ACC neurons during repetitive VTA stimulation was due to a combination of factors, in addition to a genuine dopamine effect. Some factors might include elevation of extracellular potassium from sustained neuronal activity resulting from the VTA stimulation (Levy, 1980; Nicoll, 1979; Nicoll and Alger, 1979; Walz and Hertz, 1983). The enhancement of the firing index of HIPP-ACC neurons to direct iontophoretic application of dopamine

Figure 7. Dose-response relationship of dopamine, LY171555, and SKF38393 on the firing index of HIPP-ACC neurons. The percentage change in firing index was calculated by comparing the mean value determined from the last 6 stable baseline firing indices, with the mean value of 6 firing indices obtained following iontophoretic application of the dopamine agonists. All values are expressed as means $\pm$ SEM, with the SEM drawn in one direction only for clarity. The numbers in parentheses represent the number of neurons tested. For those neurons whose baseline firing index was unaltered by SKF38393 but, instead, selectively enhanced by LY171555, their changes in firing index were compared using a paired *t* test, with asterisks indicating $p < 0.001$.

has ruled out the possibility that this was produced by the activation of the sparse dopaminergic projection from VTA to the ventral hippocampus (Ishikawa et al., 1982; Scatton et al., 1980). Furthermore, direct application of dopamine hyperpolarizes hippocampal neurons but does not increase their excitability (Bernardo and Prince, 1982a, b; Haas and Konnerth, 1983; Herrling, 1981; Stazione et al., 1984). This supports the earlier suggestion that VTA stimulation releases endogenous dopamine from the axonal terminals of dopaminergic neurons in the accumbens, which enhances the terminal excitability of HIPP-ACC neurons.

Dopamine may enhance the terminal excitability of HIPP-ACC neurons via its D1 or D2 receptors (Kebabian and Calne, 1979). The sensitivity of the terminals of HIPP-ACC neurons to the D2 agonist LY17155 but not to the D1 agonist SKF38393 suggests that D2 receptors mediated the increase in terminal excitability. Furthermore, sulpiride, a selective D2 antagonist, blocked the enhanced firing index in these neurons produced by conditioning VTA stimulation, while SCH23390, a D1 antagonist, had no effect.

Whether dopamine, or its D2 agonist and antagonist, exert their effects directly on the axonal terminals of HIPP-ACC neurons or indirectly via interneurons or a transynaptic feedback pathway from the accumbens to the hippocampus was also investigated using ibotenic acid lesions. By administering this axon-sparing neurotoxin (Kohler and Schwarcz, 1983) into the medial accumbens, most of the intrinsic accumbens neurons, as well as the soma of neurons that may feed back to the hippocampus, were destroyed. With this preparation, the firing index of HIPP-ACC neurons following VTA stimulation or iontophoretic application of dopamine or LY171555 in these rats was not significantly different from that obtained from normal unlesioned rats. These observations provide additional support for the suggestion that direct activation of dopamine D2 receptors located on the axonal terminals of the glutamatergic HIPP-ACC neurons, but not on intrinsic interneurons in the accumbens or accumbens-hippocampal pathway, are responsible for the changes in the terminal excitability of HIPP-ACC neurons.

Dopaminergic and glutamatergic neuronal interactions have also been studied extensively in the caudate nucleus, and some of the findings are relevant to the results of the present study. Dopaminergic agonists (at relatively high doses) decrease the potassium release of glutamate from striatal slices and synaptosomes (Mitchell and Doggett, 1980; Rowland and Roberts, 1980). Decortication reduces D2 type dopamine receptor binding in the rat striatum (Schwarcz et al., 1978; Theodorou et al., 1981). The striatal release of preloaded tritiated glutamate following electrical stimulation of frontal cortex efferents to the striatum is inhibited by conditioning stimulation of the nigrostriatal dopaminergic pathway (Godukhin et al., 1984). These biochemical observations complement the present findings, which suggest that D2 receptors on the afferent terminals of HIPP-ACC neurons modulate the release of glutamate from the axonal terminals by polarizing these terminals. Since the excitability of the HIPP-ACC neurons was also enhanced by extracellular iontophoretic application of potassium, a depolarizing agent, it appears that dopamine may have a depolarizing action. This mechanism is analogous to the well-studied phenomenon of primary afferent depolarization responsible for presynaptic inhibition of sensory inputs to the spinal cord (Kocsis and Waxman, 1982; Levy, 1980; Schmidt, 1971). Nevertheless, in EM studies of the nucleus accumbens, close apposition of the tyrosine hydroxylase-stained (marker for dopaminergic neurons) terminals onto striatal afferent terminals to form axoaxonic synapses with postjunctional specialization has not been observed (Arluison et al., 1984; Hassler and Chung, 1976; Pickel et al., 1981). However, dopamine may exert a nonsynaptic mode of action over a short distance (200–400 Å; Lehmann and Langer, 1983; Pappas and Waxman, 1972; Vizi, 1984) and produce a long-lasting effect. The action of dopamine is thus more appropriately termed "neuromodulation" (Lehmann and Langer, 1983).

The action of dopamine, or its D2 agonist (LY171555), as well as conditioning VTA stimulation, produced a prolonged enhancement of the firing index. Following several brief trains of pulses delivered to the VTA, or short application of the D2 agonist, recovery did not occur for up to 30 min. For a number of neurons in which no recovery was observed during the entire period of recording, the time course of this prolonged enhancement of presynaptic terminal excitability resembled that of long-term potentiation (LTP), which, in contrast, occurs in the postsynaptic sites of hippocampal afferents and some limbic forebrain pathways (Bliss and Lomo, 1973; Douglas and Goddard, 1975; Racine and Milgram, 1983; Racine et al., 1983). It is likely that the prolonged presynaptic changes of the hippocampal output neurons observed in this study reflect changes in the "plasticity" of the synaptic terminals of HIPP-ACC neurons and, thus, altered transmission patterns of this pathway.

The prolonged excitability changes following dopamine receptor activation may be associated with intracellular metabolic events such as the generation of intracellular messenger(s) that mediate a slow phosphorylation–dephosphorylation cycle of membrane ion channel proteins to gate ion fluxes and, consequently, a change in the neuronal excitability (Greengard, 1978; Hartzell, 1981; Ng and Matus, 1979; Williams and Rodnight, 1977). However, activation of striatal D2 receptors inhibits adenylate cyclase (Onali et al., 1985; Weiss et al., 1985), the enzyme that catalyzes the formation of the second messenger, cAMP. Nonetheless, other second messengers, such as the receptor-activated hydrolyzed products of membrane phospholipids, diacylglycerol and inositol triphosphate, have been suggested to be associated with neurotransmitter receptors not positively linked to adenyl cyclase (Berridge and Irvine, 1984; Onali et al., 1985). Although there is still a lack of direct evidence, it is possible that D2 receptor activation triggers a se-

quence of intracellular metabolic events involving the phospholipid messengers, leading to changes in calcium mobilization (De Vries and Beart, 1985) and ion channel protein phosphorylation that may contribute partly to a prolonged alteration of the gating properties of the ion channel(s) (Bernardi et al., 1982; Onali et al., 1985).

Dopamine has been shown to depolarize, ranging up to 20 mV, postsynaptic membranes in mammalian striatal and frontal cortical neurons, primary afferents, and spinal motoneurons (Bernardi et al., 1978, 1982; Gallagher et al., 1980; Herrling and Hull, 1980; Kitai et al., 1976; Krnjevic et al., 1978; Mercuri et al., 1985; Yim and Mogenson, 1986). This depolarization is often associated with a general decrease in membrane conductance and a clear suppression of spontaneous spike discharge. In hippocampal pyramidal neurons, however, dopamine hyperpolarizes the postsynaptic membrane (Bernardo and Prince, 1982a, b; Herrling, 1981; Suppes et al., 1985). In addition, stimulation of the autoreceptors located on the terminals of nigrostriatal dopaminergic neurons by dopamine agonists tends to suppress the excitability of these neurons, suggesting a hyperpolarizing action of dopamine on its own terminals that regulates its release (Mereu et al., 1985; Tepper et al., 1984). These findings clearly indicate that dopamine has multiple actions at different neuronal sites. The results of the present study suggest that dopamine can, via D2 receptors, depolarize the synaptic terminals of HIPP-ACC neurons (principally glutamatergic) (Walaas and Fonnum, 1979), lowering the threshold of excitation and, hence, increasing their excitability.

Finally, it is known that moderate depolarization of the axonal terminals and the associated reduction of the amplitude of subsequent action potentials invading the terminals can reduce the quantal release of transmitter (Kusano et al., 1967; Takeuchi and Takeuchi, 1962). This mechanism of presynaptic inhibition (Eccles, 1964) could partly account for the attenuating effects of the excitatory responses of accumbens neurons to hippocampal stimulation produced by activation of the mesolimbic dopaminergic system via conditioning VTA stimulation (Yang and Mogenson, 1984). This action of dopamine may contribute to a gating mechanism (Mogenson, 1984; Mogenson et al., 1980; Stevens and Livermore, 1978), which operates to "prevent" hippocampal signals (O'Keefe and Nadel, 1978; Olton et al., 1978) that are relayed via the accumbens to motor effector sites in the subpallidal basal forebrain (Mogenson, 1984; Yang and Mogenson, 1985b). In addition, considering the nucleus accumbens as one of the prime target sites responsible for the clinical actions of antipsychotic drugs that block D2 receptors (Owen et al., 1978; Seeman, 1980), the findings of this study raise questions about the possible role of the D2 receptors on limbic afferent terminals in the pathogenesis of psychosis which may be mediated, in part, through mechanisms occurring in the nucleus accumbens (Cross et al., 1981; Matthysee, 1981; Stevens, 1973).

In summary, this study has demonstrated that dopamine produced a prolonged enhancement of the terminal excitability of HIPP-ACC neurons via direct activation of its D2 receptor located on the axonal terminals of these cells. The enhancement of terminal excitability suggests a depolarizing action of dopamine, and this may contribute to the gating mechanism that regulates the quantal release of excitatory transmitter from the HIPP-ACC neuron by presynaptic inhibition.

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