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Effects of dopamine, D–1 and D–2 dopaminergic agonists on the excitability of hippocampal CA_1 pyramidal cells in guinea pig

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Summary. In hippocampal pyramidal cells (HPCs), Dopamine (DA) application (1 μM) produced, in 50% of recorded cells, an hyperpolarization of the resting membrane potential (r.m.p.) and an increase of the afterhyperpolarization (AHP) amplitude and duration in 79% of recorded cells. DA-induced effects on both the r.m.p. and AHP were mimicked by bath application of a D–1 selective agonist, SKF 38393 (20 μM). In addition, we have observed that a D–1 selective antagonist such as SCH 23390 (1 μM) abolished the action of both DA and SKF 38393. In contrast, the activation of D–2 receptors through LY 171555 (10 μm) produced, in 50% of cells, a depolarization of the r.m.p. and a depression of the AHP in 67% of recorded cells. These results suggest that the effects observed in hippocampal pyramidal neurons after DA application of micromolar concentration are mediated by D–1 subtype of receptors.

Key words: Dopamine – D–1 and D–2 agonists – Afterhyperpolarization – Hippocampal slices – Guinea pig

Introduction

Anatomical and biochemical studies have provided evidence for dopaminergic projections to the hippocampus arising from the ventral tegmental area and the medial part of substantia nigra (Simon et al. 1979; Scatton et al. 1980; Verney et al. 1985). Furthermore, specific binding studies have ascertained the presence in the hippocampus of both D–1 and D–2 subtypes of receptors (Bischoff et al. 1980; Dawson et al. 1985; Scatton et al. 1985; Schultz et al. 1985).

In addition electrophysiological experiments have suggested a modulatory role of dopamine (DA) in the hippocampus (Biscoe and Straughan 1966; Herrling 1981). In hippocampal pyramidal cells (HPCs), it has been found that DA (1 μM–10 μM) induces a small hyperpolarization of the resting membrane potential (r.m.p.) and a long lasting increase of the afterhyperpolarization (AHP) (Benardo and Prince 1982a, b; Haas and Konnerth 1983; Pockett 1985; Suppes et al. 1985; Dinan et al. 1987). The AHP is calcium-dependent and follows a train of action potentials (Alger and Nicoll 1980; Hotson and Prince 1980). It has also been reported that DA (10 μM–100 μM) is able to reduce the AHP (Stanzione et al. 1984; Malenka and Nicoll 1986), but this effect is not caused by the activation of dopaminergic receptors since it is blocked by a selective β–1 adrenoreceptor antagonist (Malenka and Nicoll 1986).

Nevertheless none of these studies has characterized the pharmacology of DA effects in its action on D–1 and D–2 subtypes of DA receptors. Therefore, the present experiments were carried out in order to clarify the contribution of D–1 and D–2 receptors in the action of DA on CA_1 pyramidal cells.

Methods

The experiments were performed on transverse slices (300–350 μm) prepared from dorsal hippocampus of guinea pigs (200–350 g). After cutting, slices were stored in a holding chamber containing Kreb's solution (30° C) and allowed to recover for at least one hour. The composition of Kreb's solution was (in mM): NaCl 124, NaH_2PO_4 1.25, $NaHCO_3$ 26, KCl 3.5, $CaCl_2$ 2, $MgSO_4$ 2, glucose 10 and was saturated with a 95%O_2–5%CO_2 gas mixture, producing a pH of about 7.4. The slices were then placed on the net of the recording chamber (volume 1.7 ml) at the interface between warm humidified gas (95%O_2–5%CO_2) and oxigenated Kreb's solution at 35–37° C. The complete replacement of the medium in the chamber occurs in one minute (flux-rate 1.7 ml/min).

Intracellular recordings were made from neurons of the CA_1 region using glass micropipettes filled with 4M potassium acetate (80–120 MΩ). The microelectrode was connected to a DC high impedance amplifier with a bridge circuit for current injection. Signals were displayed on an oscilloscope and stored on a magnetic

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tape (video recorder system) through a digital audio processor (PCM-501 ES, Sony) with a sampling frequency of 44.1 KHz. Data were analyzed off-line with a personal computer (Olivetti M28), connected to an X-Y plotter (Graphtec MP 1000). Single recordings were printed by a chart recorder (Gould instruments, model ES 1000) using a speed expander module (SPX 100) with a sampling freguency of 10 KHz.

Intracellular application of a depolarizing current pulse produced a train of action potentials and elicited an AHP whose amplitude and duration depended on the number of the action potentials and on the r.m.p. of the cell (Hotson and Prince 1980). Therefore, for every cell analyzed the intensity of the depolarizing current pulse was adjusted in order to keep constant the number of action potentials during drug application. The membrane potential was reset to the control level by passing steady direct current through the recording electrode when drug application caused changes in the r.m.p. of the cell.

Under such conditions, the amplitude and the duration of the AHP were measured before and after drug application. The amplitude was measured at the peak (AHPp) and 550 ms from the end of the pulse (AHPs). The duration (AHPd) was estimated as the interval between the end of the depolarizing current pulse and the time when the amplitude of the AHP was restored to 80% of its peak value.

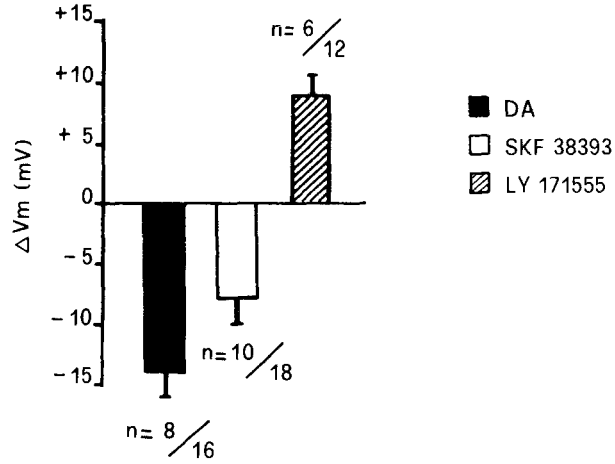

Fig. 1. Effect of DA, SKF 38393 and LY 171555 on the resting membrane potential of HPCs. Each column represents the mean value of the difference (ΔVm) between the r.m.p. of the cell before and during the maximal effect of the drugs. The n ratio represents the proportion of the cells in which we have noted a modification of the r.m.p. Vertical bars indicate s.e.m.

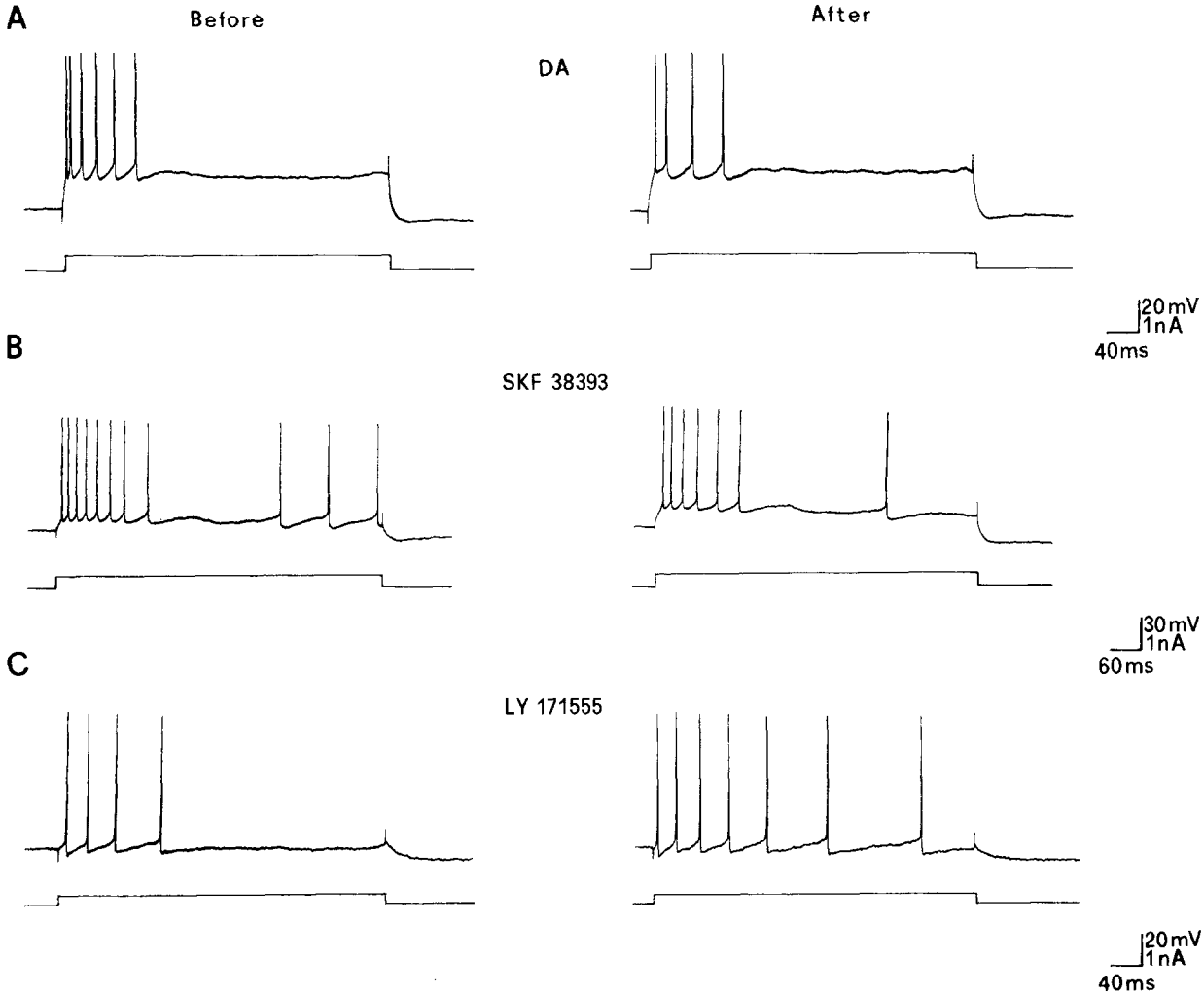

Fig. 2A–C. Effects of DA, SKF 38393 and LY 171555 on the accomodation in three typical HPCs following injection of depolarizing current pulses. Note that DA 1 μM (**A**) or SKF 38393 20 μM (**B**) increase the spike accomodation, whereas a reduction of accomodation is present after LY 171555 10 μM bath application (**C**). The resting membrane potentials of cells were −73 mV, −64 mV and −60 mV respectively. The r.m.p.s of the cells were kept constant at the control value with the injection of DC current

A statistical analysis of AHP amplitudes and duration was performed using the student's *t*-test for paired observations.

The input resistance of the cell was estimated from the voltage deflession evoked in response to hyperpolarizing current pulse of 0.5 nA in amplitude and 200 ms in duration.

The following drugs were added for 10–20 min to the Kreb's solution: dopamine (Sigma), SKF 38393 (Smith, Klein and French), LY 171555 (Ely Lilly), SCH 23390 (Schering), norepinephrine (Sigma) and Tetrodotoxin (Sigma). In order to prevent oxidation, drug solutions were prepared immediately before each application. No trace of the pink colour that indicates DA oxidation was detected at the time when electrophysiological effects were observed.

Since DA (1 μM), SKF 38393 and LY 171555 bath application induced very long lasting effects the slices were changed after each drug application.

Results

The present data have been collected from 80 CA1 neurons, identified as HPCs on the basis of physiological criteria (Schwartzkroin 1975, 1977). In our experiments neurons having r.m.p. < -60 mV, action potential amplitudes >70 mV and resting input resistances (Rin) ranging from 30 up to 40 MΩ, have been selected.

The great majority of the cells recorded had no spontaneous activity. The response of HPCs to long depolarizing current pulses (400 ms) were characterized by an action potential discharge with a progressive increase of interspike intervals, and no or few spikes in the last part of the pulse (Fig. 2A–C). This phenomenon has been called accomodation (Madison and Nicoll 1984).

Application of DA (1 μM) or the D–1 agonist SKF 38393 (20 μM) caused hyperpolarization of the r.m.p. in 50% of the tested cells, whereas the D–2 agonist LY 171555 (10 μM) induced a consistent depolarization in 50% of the cells. As shown in Fig. 1 the maximum averaged hyperpolarization measured was 14 ± 2 mV (average $\pm$ s.e.m.) and 8 ± 2 mV after DA or SKF 38393 application respectively, whereas the mean of the maximum values of depolarization induced by LY 171555 was 9 ± 2 mV.

These changes in membrane potential appeared 5–10 min after the beginning of drug application and reached maximum values after several minutes, leaving the Rin of the cell unchanged.

An increase of spike accomodation was often observed after bath application of DA (1 μM) or SKF 38393 (20 μM). As shown in Fig. 2A, B this effect was characterized by both an increase of the interspike interval of the initial train of action potentials and by a reduction or block of spike generation during the last part of the pulse. A full recovery of the number of spikes was obtained by increasing the amount of current injected (data not shown). In contrast, LY 171555 (10 μM) increased the frequency of action potentials discharge both in the initial burst and in the last part of the pulse (Fig. 2C).

These changes in the accomodation of cell discharge were independent of the effect on the r.m.p. because they were also present when the r.m.p. of the cell was kept to the control level by passing steady direct current through the recording electrode.

In 79% of the recorded cells ($n = 14$), the AHP evoked by depolarizing current pulse was greatly enhanced in duration and amplitude after 1 μM DA application. Such an increase of AHP was also obtained in cells in which DA application did not change the r.m.p. of the cell. A typical effect of DA on a HPC is shown in Fig. 3A. In this cell before DA application the AHP had a peak-amplitude of about 3 mV and a duration of 1.5 s (Fig. 3A, left trace). Fifteen min after drug application the AHP was of larger amplitude (9 mV at the peak) lasting as long as 2.7 s (Fig. 3A, right trace). We never observed changes of the Rin of cells at the time when the increase of the AHP reached the maximum value.

As shown in the histograms of Fig. 3B (after 1 μM DA application) the mean values of the AHPp, AHPs

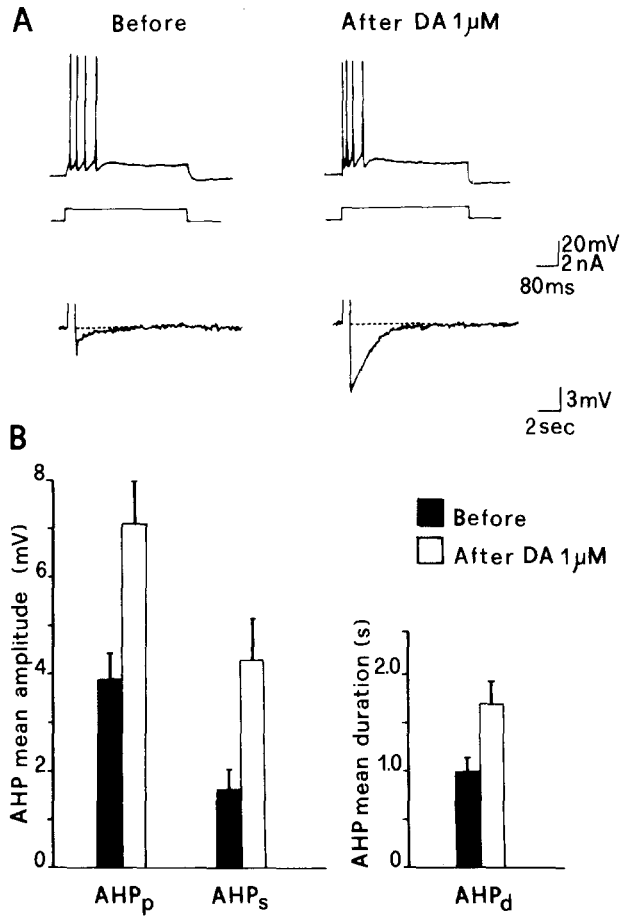

Fig. 3A, B. Bath application of DA (1 μM) for 20 min enhances the AHP in HPCs. **A** Upper traces show a response of HPC to a depolarizing current pulse (400 ms, 0.5 nA), before and 15 min after DA application. **A** Lower traces show the afterhyperpolarizations that follow the end of the depolarizing pulses delivered at 0.1 Hz. Each trace represents the average of ten individual sweeps. The r.m.p. of the cell (broken line) was -66 mV and was kept constant during drug application with a DC current injection. **B** Histograms show the cumulative effect of 1 μM DA on the AHP in 11 HPCs. Each column represents the mean values of the AHP amplitudes (AHPp, AHPs) and the AHP duration (AHPd) measured before (black columns) and at the time of maximum effect of this catecholamine (white columns). The increase of AHPp, AHPs amplitudes and AHP duration after DA application is clearly depicted. The differences are significant at $p < 0.005$ (see methods). Vertical bars indicate s.e.m.

and AHP duration increased significantly from 3.9±0.5 (average±s.e.m.) mV. 1.6±0.4 mV and 1.0±0.1 s to 7.1±0.9 mV, 4.3±0.8 mV and 1.7±0.2 s.

The enhancement of the AHP started within 10–20 min after drug application, reaching the maximum value from 5 to 40 min from the beginning of the wash out. Recovery of the AHP did not occur during a single impalement even though it was possible to follow the cell activity over a period of about two hours in some cells.

In contrast the AHP remained unchanged for a comparable period of time when the slice was perfused only with Kreb's solution. To verify whether the lack of recovery of the AHP reduction, after 1 μM DA application, could depend on our experimental conditions, a series of experiments were performed with bath application of DA (100 μM) or norepinephrine (NE) (10 μM), known to activate β–1 adrenergic receptors (Madison and Nicoll 1986a, 1986b; Malenka and Nicoll 1986). In every cell analyzed ($n=10$) we observed that after the bath application of DA or NE the decrease of spike accomodation and the reduction of the AHP recovered soon after the wash out (Fig. 4A, B).

In order to determine which subtype of DA receptor was responsible for DA effects on the AHP, slices were perfused with SKF 38393 or LY 171555, selective D–1 and D–2 agonists. We observed that in 69% of the HPCs ($n=16$) bath application of SKF 38393 (20 μM) increased the AHP. An example of such an effect is illustrated in Fig. 5A, where SKF 38393 produced both a suppression of the firing in the last part of the pulse and a clear cut enhancement of AHP in amplitude and duration. The histograms of Fig. 5B show that the AHPp and AHPs mean amplitudes and AHP mean duration increased significantly from 5.0±0.4 (average±s.e.m.) mV 3.0±0.4 mV and 1.2±0.2 s to 8.6±0.9 mV, 5.8±0.6 mV and 2.1±0.2 s.

The enhancement of the AHP observed after SKF 38393 was detectable during the first five minutes,

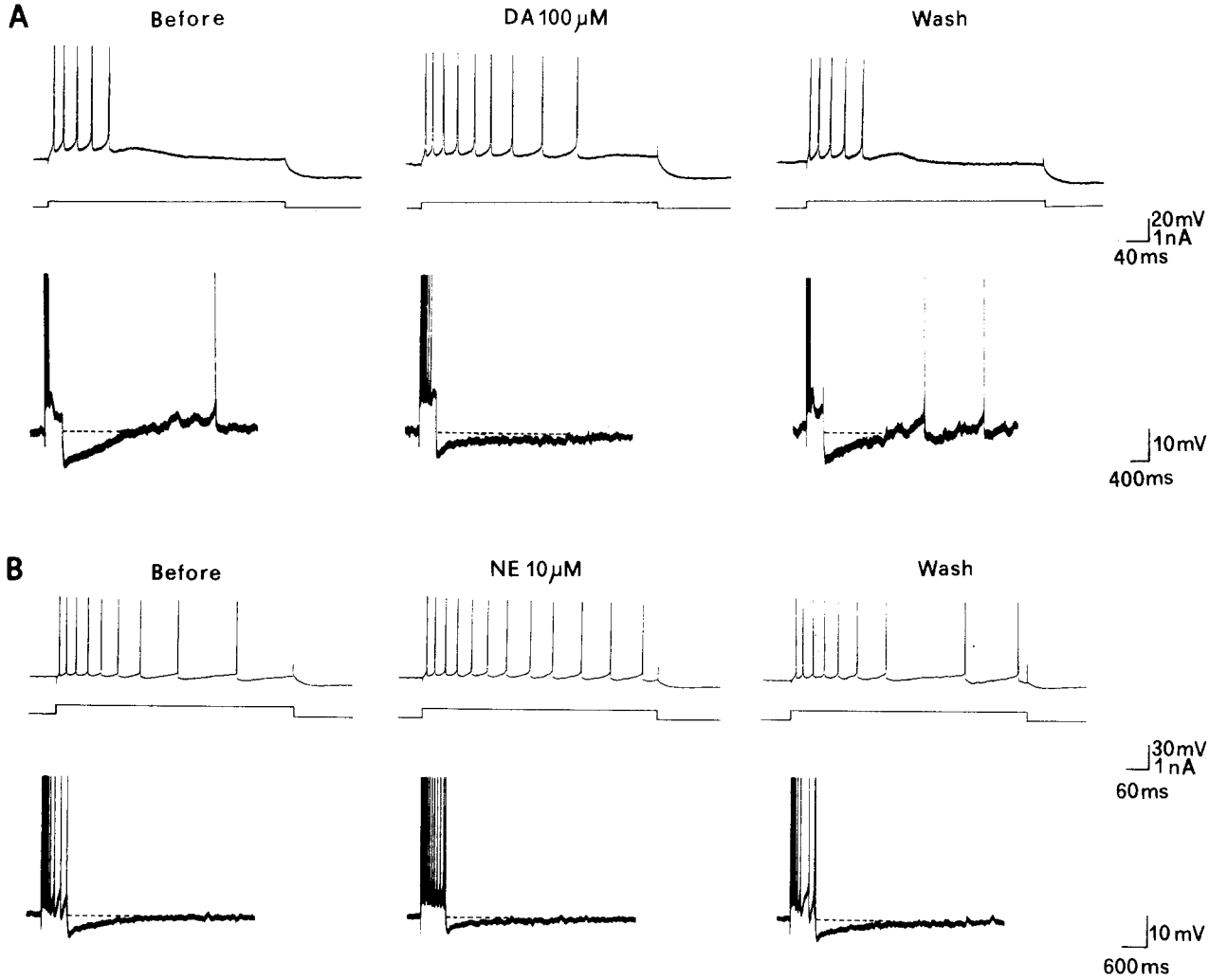

Fig. 4A, B. Activation of β–1 adrenoreceptors reduces the AHP in HPCs. **A** Upper traces show the spike accomodation during DA (100 μM) bath application. Lower traces show, in the same cell, the AHP that follows the depolarizing pulse. There is a clear reduction of the AHP both in amplitude and in duration, concomitant with the reduction of spike accomodation. The r.m.p. of the cell (broken line) was −69 mV. **B** Bath application of NE (10 μM) induces a reversible reduction of spike discharge accomodation (upper traces) and a parallel reduction of the AHP (lower traces). The r.m.p. of the cell (broken line) was −65 mV. The effects induced by both drugs recovered completely within 10 min from the beginning of the wash out

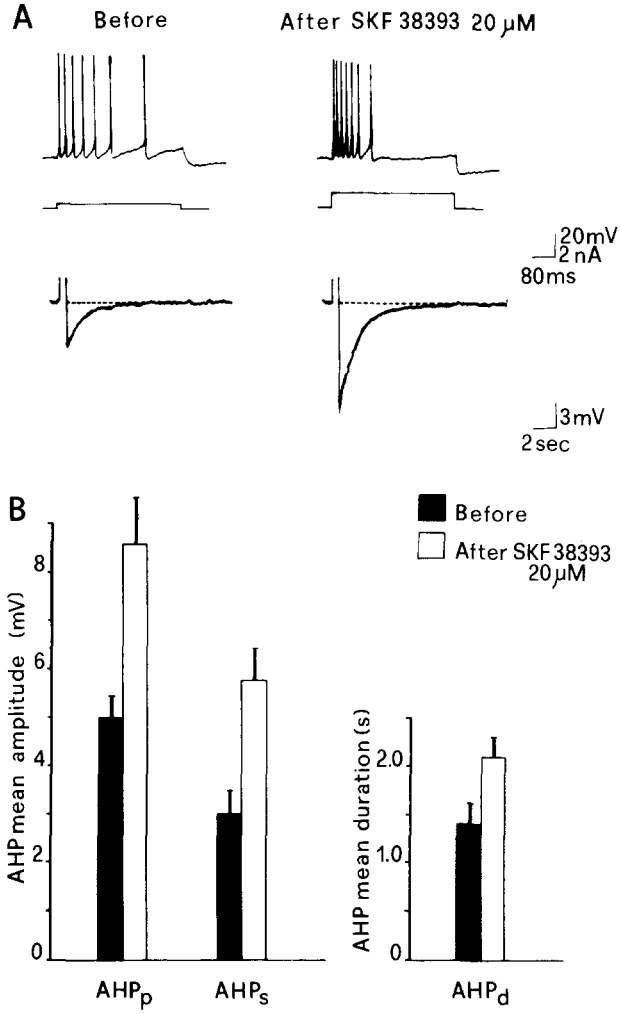

Fig. 5A, B. SKF 38393 (20 μM) enhances the AHP in HPCs. **A** Upper traces show single records of HPC responses to a depolarizing current injection (0.1 Hz) before and after SKF 38393 bath application. Note that after SKF 38393 the value of the depolarizing current pulse was increased to obtain the same number of action potentials that were evoked before drug application. Lower traces represent the averages of ten individual sweeps recorded from the same cell at the same time of the upper ones to show the enhancement of the AHP. The r.m.p. of the cell (broken line) was −70 mV. **B** Histograms showing the cumulative effects of SKF 38393 (20 μM) on the AHP in 11 HPCs. The columns represented the mean values of the AHP amplitudes (AHPp, AHPs) and AHP duration (AHPd) measured before (black columns) and during (white columns) the maximum effect of the drug. Note that SKF application, significantly, increases the AHPp, AHPs amplitudes and AHPd duration. The differences are significant at $p<0.005$. Vertical bars indicate s.e.m.

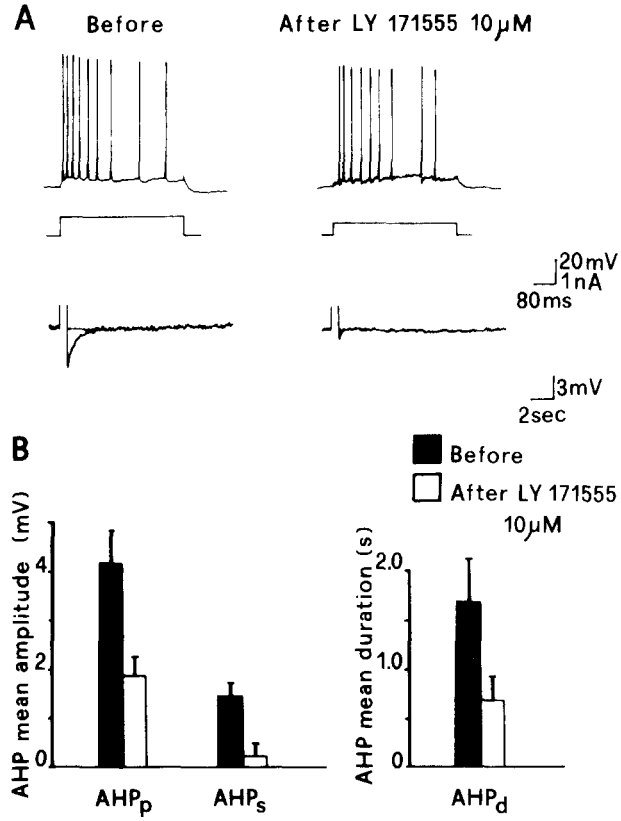

Fig. 6A, B. Reduction of the AHP induced by LY 171555 (10 μM) bath application. **A** Upper traces show a response of HPC to a depolarizing current injection (0.1 Hz), before and after LY 171555 application. Note that after LY application the current was reduced to obtain the same number of spikes as in the control. Lower traces represent the averages of ten individual sweeps showing the AHP that follows the same depolarizing current pulses represented in the corresponding upper traces. The resting membrane potential of the cell (broken line) was −75 mV. **B** Histograms showing the effects of 10 μM LY on the AHP in 14 HPCs. The columns represented the mean values of the AHP amplitudes (AHPp, AHPs) and AHP duration (AHPd) measured before (black columns) and during (white columns) the maximum effect of the drug. There is a clear reduction of AHPp, AHPs amplitudes and AHPd duration. The differences are significant at $p<0.005$. Vertical bars indicate s.e.m.

reached the maximum value after several minutes and did not recover during the observation period of about one hour.

In contrast in 67% of the HPCs ($n=12$), LY 171555 (10 μM) clearly reduced the AHP. A typical block of the AHP is evident in the cell illustrated in Fig. 6A.

The AHPp and AHPs mean amplitudes and AHP mean duration decreased from 4.2 ± 0.6 mV, 1.5 ± 0.2 mV and 1.7 ± 0.4 s to 1.7 ± 0.3 mV, 0.3 ± 0.2 mV and 0.7 ± 0.2 s (Fig. 6B). The delay of this effect was approximately 5 min, whereas the maximal reduction was observed 15 min after the beginning of the wash out.

To analyze further the effects of DA on D–1 and D–2 subtypes of receptors, in eight cells the effects of DA were tested in slices preincubated for 20 min with SCH 23390 (1 μM), a selective D–1 antagonist (Hyttel 1983).

In cells recorded during SCH 23390 perfusion, no detectable changes were observed either in the r.m.p. or in the AHP. However, in all cells tested ($n=8$), SCH 23390 counteracted the DA induced hyperpolarization of the r.m.p. and the enhancement of the AHP. Moreover in four out of eight cells, DA application in the presence of SCH 23390 clearly reduced the AHP amplitude and duration. In another eight cells, SCH 23390 antagonized the enhancement of the AHP usually induced by SKF 38393 application.

The effects of DA, SKF 38393 and LY 171555 on the AHP were also tested in the presence of tetrodotoxin (TTX) (n = 8). Bath application of TTX (1 μM) eliminated fast sodium-dependent spikes and revealed a voltage-sensitive calcium-spike (Schwartzkroin and Slawsky

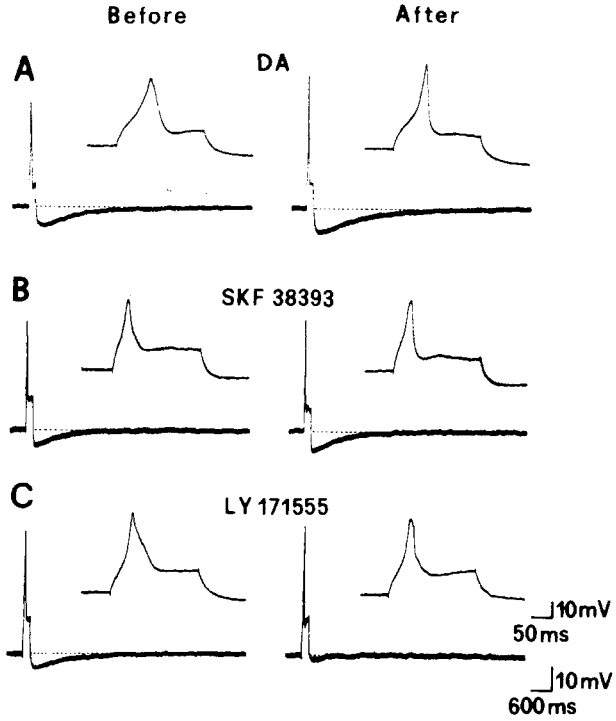

Fig. 7A–C. Effects of DA, SKF 38393 and LY 171555 on the AHP in a 1 μM TTX-containing medium. The AHP was evoked by depolarizing current pulse of 200 ms in duration (**A–C**) and 0.5 nA (**A, B**), 0.4 nA (**C**). Upper panels: current-clamp recorded Ca^{++} spikes are shown at a faster chart speed. The resting membrane potentials of cells were −61 mV, −71 mV and −74 mV, respectively, for **A–C**

1977). The block of sodium spike began within 5–10 min after the addition of TTX (1 μM), and started to recover 10 min after the wash out. Under this condition the AHP was still increased by DA (1 μM) or SKF 38393 (20 μM) and reduced by LY 171555 (10 μM) (Fig. 7A–C).

Discussion

The major new finding of this study is that DA acting via D–1 receptors can increase the amplitude and duration of the afterhyperpolarization in HPCs. Conversely activation of D–2 receptors appears to produce a depression of the AHP.

The hyperpolarization of the r.m.p. observed in our experiments after DA application has been reported in previous studies (Benardo and Prince 1982a, b; Haas and Konnerth 1983; Suppes et al. 1985). It has been suggested that this effect is due to the increase of a Ca^{++}-dependent potassium conductance (Benardo and Prince 1982a, b).

Our findings that in some cells, DA application induces a clear AHP augmentation whereas the r.m.p. remains unchanged, might imply that at the r.m.p. the Ca^{++} conductance is not fully activated (Hotson et al. 1979) and therefore $[Ca^{++}]_i$ is too low for DA action (Benardo and Prince 1982b).

The hyperpolarization of the r.m.p. observed in our experiments after application of SKF 38393, could represent the basis for the long lasting depression of the spontaneous neuronal firing observed after SKF 38393 application (Smialowski and Bijak 1987). The similarities between the effects of DA and SKF 38393 on the r.m.p., and the block induced by SCH 23390 suggest that this effect is probably mediated by an interaction of this catecholamine with D–1 subtype of receptors. We have also observed that LY 171555 produces a depolarization of the r.m.p. This result may explain the excitatory effect of LY 171555 on the firing rate of HPCs described by Smialowski and Bijak (1987).

In addition our study shows that, independently of the effect on the r.m.p., both DA and SKF 38393 reduce the number of spikes evoked by a depolarizing current pulse. Since a calcium dependent potassium conductance is also involved in producing the accomodation (Hotson and Prince 1980), enhancement of this conductance by DA or SKF 38393 may explain the effects observed on the accomodation. In neostriatal neurons it has been reported that DA (1–10 μM) and SKF 38393 (1–10 μM) produce a decrease in the number of action potentials evoked by depolarizing pulses. This inhibitory action of DA is coupled with a decrease of the anomalous rectification which is mainly caused by the activation of a persistent sodium current (Calabresi et al. 1987).

We have found that DA (1 μM) significantly increases the AHP, a finding consistent with the observations of other authors (Benardo and Prince 1982a, b; Haas and Konnerth 1983; Pockett 1985; Dinan et al. 1987). It has also been reported that neuroleptic drugs, that are traditionally viewed as DA-antagonists (Bischoff et al. 1979), decrease the AHP in hippocampal CA1 pyramidal neurons (Dinan et al. 1987). The effect of DA on the AHP provides evidence that its enhancement in amplitude and duration may result from the activation of D–1 subtype of dopaminergic receptors. In fact SKF 38393, a highly selective agonist of D–1 receptors (Stoof and Kebabian 1981), mimicks the effects of DA; the action of both DA and SKF 38393 on the AHP were clearly abolished in slices preincubated with SCH 23390.

In our experiments we observed that the activation of D–2 receptors through LY 171555 produces a depression of the AHP. Treatment with TTX did not block the effect of DA, SKF 38393 and LY 171555 on the AHP, suggesting a direct postsynaptic action of these drugs on the cell recorded.

The long term modifications of the AHP observed after DA, SKF 38393 and LY 171555 application could not be due to deterioration of the slices or of the recorded cells, as AHP amplitude and duration remained unchanged for a comparable period of time during control experiments. On the other hand, we always obtained a reversible reduction of the AHP, when DA or NE interact with β–1 adrenoceptors.

The sustained increase of the AHP after DA (1 μM) or SKF 38393 (10 μM) applications suggests a chain of intracellular events starting with the activation of D–1 receptors, leading to an increase of second messenger levels and in turn to modulation of a Ca^{++}-dependent potassium conductance. It is well known that in neostriatum D–1 receptors are positively linked to an adenylate cyclase which increases cAMP levels, while stimulation

of D–2 receptors reduces cAMP formation (Stoof and Kebabian 1981).

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