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Muscarinic receptors modulate the afterhyperpolarizing potential in neostriatal neurons

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Abstract

The actions of carbachol were studied on the firing response of neostriatal neurons recorded intracellularly from in vitro slice preparations of the rat brain. Carbachol (1–10 μM) reversibly reduced the afterhyperpolarization in neostriatal neurons. This effect was accompanied by an increase in both firing frequency and input resistance in the subthreshold voltage range. Atropine (1–10 μM) reversibly blocked carbachol effects, suggesting muscarinic receptor modulation. Pirenzepine (up to 1 μM), but not AF-DX 384 (10 μM) or gallamine (30 μM), blocked the effects of carbachol on the afterhyperpolarization. The protein kinase C activator, phorbol 12,13 dibutyrate, but not the inactive phorbol ester, 4α-phorbol 12-myristate 13-acetate, mimicked carbachol effects. The results suggest that muscarinic receptors, probably of the M_1 type, regulate neostriatal excitability by modulating afterhyperpolarization.

Keywords: Muscarinic receptor; Firing pattern, modulation; Afterhyperpolarization; Neostriatum; Neuromodulation

1. Introduction

A variety of K^+ conductances are responsible for shaping response firing patterns in brain neurons (Connor, 1985; Rudy, 1988). These K^+ conductances are also known to be modulated by transmitters and peptides through G-protein-mediated pathways (Brown, 1990). In particular, the various conductances that make up the afterhyperpolarizing potential are a preferred target for neuromodulators in many neuronal classes of the mammalian brain (see North, 1989 and Nicoll et al., 1990 for reviews). Since the afterhyperpolarizing potential regulates firing pattern and frequency as well as the threshold level for repetitive firing (e.g., Madison and Nicoll, 1984; Storm, 1989; Galarraga et al., 1989; Pineda et al., 1992; Bielefeldt and Jackson, 1994), its modulation might provide a variety of ways to set the excitability level of neurons and networks (e.g., Connor, 1985; North, 1989; McCormick, 1993; Steriade, 1993).

Acetylcholine is a neuromodulator through a variety of muscarinic receptors (Bonner, 1989; Hulme et al., 1990; McKinney, 1993; Brann et al., 1993). It commonly displays many actions in a single class of neurons (North, 1989). It has been shown to modulate the afterhyperpolarizing potential in many brain neurons (North, 1989; Nicoll et al., 1990). The neostriatum possesses muscarinic receptors, cholinergic interneurons and much of the brain's acetylcholine (Vilaró et al., 1993; Di Chiara and Morelli, 1993; Wilson et al., 1990; Kawaguchi, 1993). Spiny projection neurons, which constitute about 90% of all the neurons in the nucleus (Wilson et al., 1990; Kawaguchi, 1993), express muscarinic m_1 and m_4 cloned receptor subtypes (Vilaró et al., 1993; Brann et al., 1993). Both cloned receptor subtypes exhibit sensitivity to pirenzepine antagonism (Hulme et al., 1990; Caulfield et al., 1993; McKinney, 1993; Quirion et al., 1993).

On the other hand, acetylcholine receptor antagonists have been of clinical use in motor disorders which involve basal ganglia pathology (Stoof et al., 1992; Riederer et al., 1993; McKinney, 1993). However, the relative scarcity of electrophysiological information about cholinergic actions on neostriatal neurons does not justify the development of new clinical trials with more specific agents (Stoof et al., 1992; Riederer et al., 1993; Di Chiara and Morelli, 1993; McKinney, 1993). A

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reduction of both Ca^{2+} plateau potentials (Misgeld et al., 1986) and Ca^{2+} currents (Howe and Surmeier, 1995) would predict effects on afterhyperpolarization and firing pattern. However, cholinergic effects on these events have not been described. Also, a cholinergic-induced depolarization, accompanied by an increase in input resistance has been reported (Dodt and Misgeld, 1986), but with no firing correlation. Therefore, this work aimed to answer a basic question: does cholinergic activation change the firing pattern by affecting a basic ionic mechanism, such as for example, the afterpotential? The experiments presented showed that the acetylcholine receptor agonist, carbachol, reduces the afterhyperpolarization. This effect produced an increase in excitability.

Part of these results have been reported in abstract form (Pineda et al., 1993).

2. Materials and methods

2.1. Preparation

Our protocol follows the recommendations from the declaration of Helsinki regarding the use and care of animals and has been described in previous work (e.g., Pineda et al., 1992). Briefly, adult (> 3 months) male or female albino Wistar rats were anesthetized and decapitated. Sagittal neostriatal slices (400 μm) were recorded when totally submerged at 30–34°C. The bathing solution was (in mM): 125 NaCl, 3.0 KCl, 1.0 $MgCl_2$, 2.0 $CaCl_2$, 25 $NaHCO_3$ and 11 glucose. The solution was saturated with 95% O_2-5% CO_2 (300 mOsm/l, pH 7.4, 30–34°C). Intracellular recordings were carried out with micropipettes filled with K-acetate 3M. Electrode d.c. resistances ranged from 80 to 120 MΩ. Intracellular recordings were made with a high input impedance electrometer with an active bridge circuit using standard techniques. The resting membrane potential and input resistance of the sample cells were approximately: < -75 mV and 50 MΩ respectively (Galarraga et al., 1994).

2.2. Stimulation protocols

Brief (up to 10 ms) intracellular current injections were used to study the afterhyperpolarization after a single action potential (see Pineda et al., 1992). The stimulus was of threshold intensity, the spike being elicited at the end of the stimulating current (Fig. 1). Events were recorded at a holding membrane potential of ≈ -60 mV, by adjusting a constant current. Bridge balance as well as recovery periods (without d.c. current) were monitored between sample records. Individual digitized records were sent to a PC computer for graphing and printing. Unless stated otherwise, records

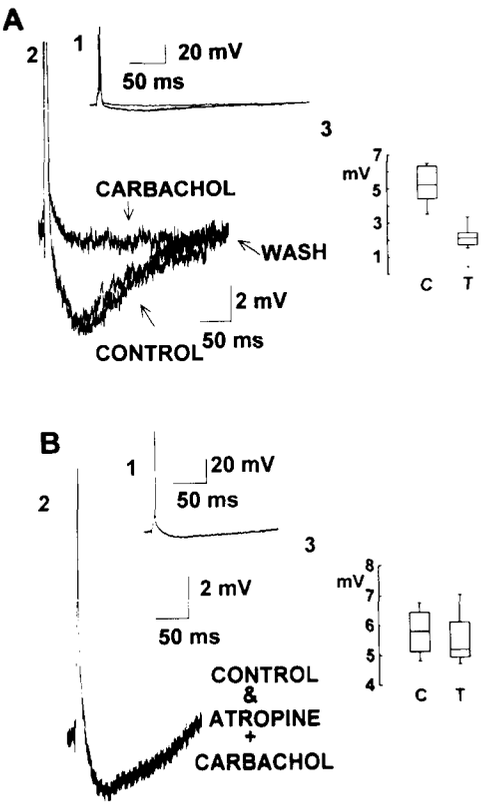

Fig. 1. Carbachol reduces afterhyperpolarization amplitude in neostriatal neurons. A: (1) Short current pulses (not shown) evoke single action potentials followed by the corresponding afterhyperpolarizing potentials before, during and after carbachol (10 μM). (2) Afterhyperpolarizations are shown at higher magnification. (3) Box plots compare afterhyperpolarization amplitudes before (C = control) and during 10 μM carbachol (T = test) in a sample of 9 neurons. B: Atropine (1 μM) blocks the effects of carbachol (10 μM) on the afterhyperpolarization (C = control, T = carbachol + atropine).

from the same neurons were compared before and after 15 min of drug application. Numerical results were obtained from the average of 7–12 digital recordings in each case. Afterhyperpolarization amplitude was measured from the holding membrane potential to the most negative peak. Long intracellular current ramps (0.05–0.075 nA/s, to get $\approx$ 0.02–0.05 V/s) were applied to measure frequency responses. Frequency-intensity (F-I), frequency-time (F-t), and current-voltage (I-V) plots were approximated with this method (see Galarraga et al., 1994). A stimulus which elicited several action potentials was compared before and during treatment. The afterhyperpolarization amplitude was a normally distributed variable. Both Student's t and/or Mann-Whitney's U statistics were used to find statistical significance among treatments, and box plots were used to illustrate these differences (for a discussion on box plots see Bargas et al., 1994).

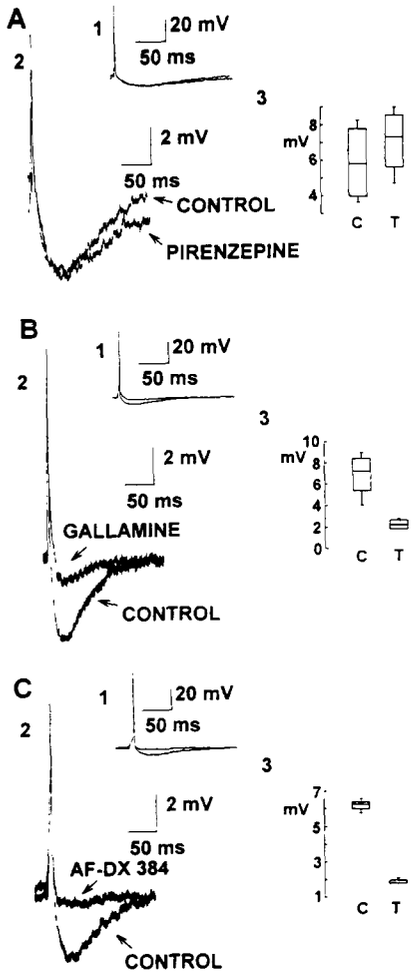

Fig. 2. Effect of carbachol is mediated by muscarinic M_1-like receptors. A: Pirenzepine (1 μM) blocks the effects of carbachol (10 μM) on the afterhyperpolarization (C = control, T = carbachol + pirenzepine). B: Gallamine (20 μM) does not impede carbachol effects (10 μM) on the afterhyperpolarization (C = control, T = carbachol + gallamine). C: AF DX 384 (10 μM) does not block carbachol (10 μM) effects (C = control, T = carbachol + AF-DX 384).

2.3. Drugs used

Carbachol, atropine (from Sigma), pirenzepine, gallamine, AF DX 384, phorbol 12,13-dibutyrate (PDB), and 4α-phorbol 12-myristate 13-acetate (4α-PMA) (all from RBI) were dissolved from stock solutions into the superfusion saline. Since it is known that low doses of phorbol esters need a long time to act, e.g., 1 μM PDB needs about 1 h to block the afterhyperpolarization in our recording conditions (see also Malenka et al., 1986; Brown and Adams, 1987), high PDB concentrations (9–15 μM) were used in order to see the effects in $\leq$ 15 min. This is necessary to maintain recording stability in small cells and to compare the results between cells.

3. Results

Fig. 1 illustrates a single action potential followed by its afterhyperpolarization (Fig. 1A1). The action potential was evoked by a step current pulse (not shown, see Materials and methods). The afterhyperpolarization is shown at greater magnification in Fig. 1A2. The mean for afterhyperpolarization amplitude evoked at ≈ -60 mV was ($\mu \pm$ S.E.M.; unless stated otherwise): -5.75 ± 0.24 mV ($n = 31$). The same figure design is followed in Fig. 2 and Fig. 3. In the example illustrated, superimposed records signaled by arrows show that carbachol (10 μM) reduced the afterhyperpolarization. This effect was seen in less than 2 min and measurements were done at 3–4 min. After this time, the effect remained as long as carbachol was left in the superfusion (e.g., > 30 min). The change was reversible (Fig. 1) in about 15 min of washing. The effect illustrated in Fig. 1 was particularly marked but was not uncommon (see box plot in Fig. 1A3). Also, carbachol action was seen in most cells tested (15/16; 94%) at 1–10 μM concentrations. The mean percentage reduction in af-

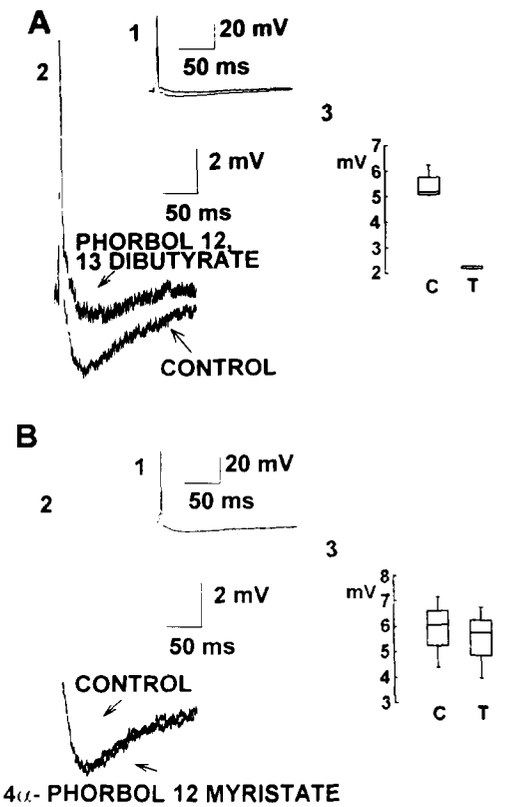

Fig. 3. Activation of protein kinase C mimics carbachol effects. A: The protein kinase C activator, phorbol 12,13 dibutyrate (15 μM), mimics carbachol effects on the afterhyperpolarization (C = control, T = phorbol 12,13-dibutyrate). B: Other phorbol ester without protein kinase C activating actions, 4α-phorbol 12-myristate 13-acetate (15 μM), has no activity (C = control, T = 4α-phorbol 12-myristate 13-acetate).

terhyperpolarization after 10 μM carbachol was to 47.3 $\pm$ 11% ($P < 0.01$) of the control value ($n = 9$) (Fig. 1A3; C = control, T = treatment, in all figures). Fig. 1B shows that when carbachol (10 μM) was administered in the presence of atropine (1 μM), it was no longer able to reduce the afterhyperpolarization ($n = 4$). This result suggests that this modulation is mediated by muscarinic receptors.

Also in the presence of pirenzepine (1 μM), carbachol (10 μM) was no longer able to reduce the afterhyperpolarization (Fig. 2A1,2) ($n = 4$). On the contrary, with pirenzepine there was a small tendency for the afterhyperpolarization to increase in amplitude (Fig. 2A2,3), suggesting a tonic cholinergic action (North, 1989). In contrast to pirenzepine, gallamine (20 μM) ($n = 4$) or AF DX 384 (10 μM) ($n = 3$), did not block the ability of carbachol (10 μM) to reduce the afterhyperpolarization (Fig. 2B,C). Although more complete concentration-response plots are needed to assess these effects, the data suggest that, as in other brain neurons (North, 1989; Nicoll et al., 1990), pirenzepine-sensitive, or muscarinic M_1 receptors, are in charge of the afterhyperpolarization modulation.

The protein kinase C activator, phorbol 12,13-dibutyrate (PDB) (9–15 μM), mimicked carbachol effects on the afterhyperpolarization (Fig. 3A). A phorbol analog without activity on protein kinase C, 4α-phorbol 12-myristate 13-acetate (4α-PMA) (15–30 μM), had no effect (Fig. 3B).

A depolarizing ramp (Galarraga et al., 1994) was given before and during carbachol to see if the reduction in afterhyperpolarization correlated with an increase in firing frequency (Galarraga et al., 1989; Pineda et al., 1992). In Fig. 4A, a neuron was depolarized from resting potential (≈ -80 mV) to evoke repetitive firing. Carbachol (10 μM) increased the firing frequency for the same stimulus by $\approx 100\%$ ($n = 3$) (Fig. 4C). A comparison of the slopes of the current-voltage functions taken from the same responses (see Galarraga et al., 1994) shows that carbachol also increased input slope resistance in the subthreshold range (see also Dodt and Misgeld, 1986) (Fig. 4B). Current, but not voltage threshold, changed after carbachol (Fig. 4C) (both traces in Fig. 4B were cut at carbachol's current threshold). Thus, the frequency boost cannot solely be attributed to a decrease in the afterhyperpolarization but also to the closing of subthreshold conductances. Then, in order to isolate the action on the afterhyperpolarization, the same experimental protocol was followed from more depolarized holding potentials (Fig. 5A). However, from depolarized potentials (> -60 mV), a depolarizing stimulus would frequently induce high frequency membrane potential oscillations preceding firing (Fig. 5A arrow). These oscillations may be induced by the alternating activation of inward sodium and transient outward potassium conductances (Bargas et al., 1989). Note that the frequency-intensity relation reflects the underlying oscillation. Thus, this phenomenon would make it difficult to see reproducible carbachol effects when using square current pulses (e.g., Dodt and Misgeld, 1986). Nevertheless, using a ramp stimulus, a significant frequency increase of $\approx 30\%$ could still be detected in the presence of

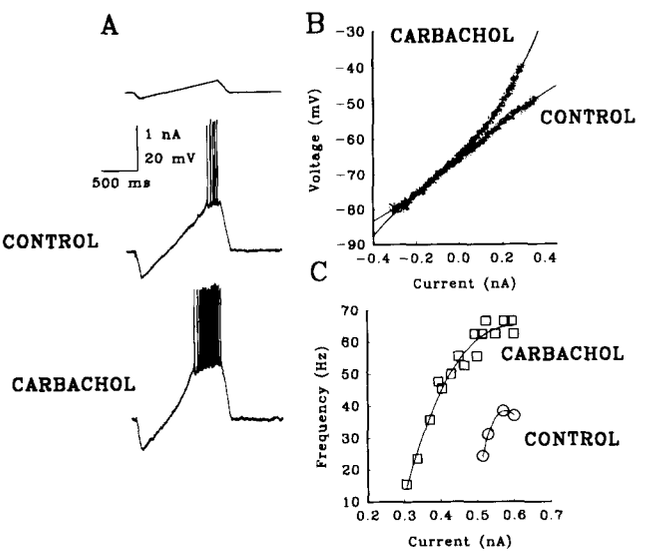

Fig. 4. Carbachol increases firing frequency response from hyperpolarized holding potentials. A: Top, current stimulus; middle, membrane potential response to a current ramp; bottom, response to the same stimulus during 10 μM carbachol. B: I-V plots using subthreshold ascending ramp responses in A. Note an increase in slope (input resistance) during carbachol. C: F-I plots before (circles) and during (squares) carbachol. Plots were taken from records in A.

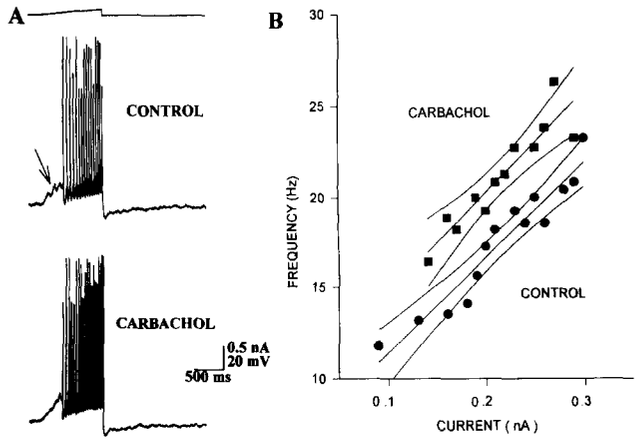

Fig. 5. Carbachol increases firing frequency response from depolarized holding potentials. A: Top, current stimulus; middle, membrane potential response to a current ramp; bottom, response to the same stimulus during 10 μM carbachol. Arrow shows membrane potential oscillations frequent at > -60 mV. B: F-I plots before (circles) and during (squares) carbachol. Note that membrane potential oscillations underlie the frequency response. Straight lines and 99% confidence intervals were fitted to the experimental points.

carbachol at −60 mV ($n = 4$; Fig. 5B). Although ramps are a better mimic of physiological activation in these cells (Galarraga et al., 1994), with these experiments it is hard to know how much of the frequency boost is due to afterhyperpolarization blockade.

4. Discussion

The present results demonstrated that firing in neostriatal neurons can be modulated by acetylcholine through muscarinic receptors. Carbachol (1–10 μM) reduced the afterhyperpolarization amplitude and this correlated with an increase in firing frequency to the same stimulus (see Galarraga et al., 1989; Pineda et al., 1992). The effect was blocked by atropine (1 μM) and pirenzepine (1 μM) but not by gallamine or AF DX 384 given at higher concentrations. Therefore, it was probably mediated by muscarinic M_1 receptors (Hulme et al., 1990; Dörje et al., 1991; McKinney, 1993; Quirion et al., 1993). More detailed experiments are needed to find out if all the effect is direct, what type of receptor and G-protein is involved, and the order of potency of agonists and antagonists. Only such more detailed studies will achieve pharmacological identification of the receptor. Furthermore, by showing that changes in frequency induced by carbachol are less prominent if stimulus occurs at depolarized potentials, frequency-intensity plots confirm that cholinergic modulation has multiple targets in these neurons (Dodt and Misgeld, 1986; Brann et al., 1993; Vilaró et al., 1993; Howe and Surmeier, 1995). Some of these actions may be synergic, so that only part of the frequency boost can be attributed to the reduction of the afterhyperpolarizing potential. These results also showed that cholinergic actions depend on membrane potential.

Since the actions studied, firing and afterhyperpolarization, are blocked by tetrodotoxin or Ca^{2+} channel blockers (Pineda et al., 1992; Galarraga et al., 1994), common tests for direct effects, i.e., the use of tetrodotoxin or Ca^{2+} channel blockers during agonist action, are not suitable in the present conditions. Nevertheless, preliminary experiments using the whole-cell voltage-clamp technique confirm the results reported here (Pineda et al., 1994, and unpublished results). On the other hand, it is known that carbachol directly reduces outward currents in isolated neostriatal neurons (Kitai and Surmeier, 1993). Also, the actions on afterhyperpolarization, as well as the activation of the phospholipase C pathway, have been demonstrated to be mediated by G-protein-coupled receptors of the postsynaptic membrane in various brain neurons (North, 1989; Nicoll et al., 1990; McKinney, 1993).

Neostriatal medium spiny neurons preferentially express muscarinic m_1 and m_4 cloned receptors (Vilaró et al., 1993; Brann et al., 1993). When tested in expression systems and cell preparations, both muscarinic m_1 and m_4 receptors are blocked by pirenzepine at similar concentrations (Hulme et al., 1990; Caulfield et al., 1993; Brann et al., 1993; McKinney, 1993; Quirion et al., 1993; Vilaró et al., 1993). Thus, both receptor clones could be seen as muscarinic M_1 receptors with the present pharmacological tools. However, some available information may allow to differentiate muscarinic M_1 from putative muscarinic M_4 receptors (Hulme et al., 1990), if the cloned receptors turn out to correspond to the pharmacologically defined receptors: first, muscarinic m_4 receptors are sensitive to both pirenzepine and AF DX 116 or 384 (Hulme et al., 1990; Quirion et al., 1993; Caulfield et al., 1993). Second, muscarinic m_1 but not m_4 receptors are known to be strongly linked to the phospholipase C pathway (Bonner, 1989; Ross, 1992; McKinney, 1993) which is activated by acetylcholine receptor agonists in neostriatal slices in conditions very similar to ours (Góngora et al., 1988). Third, although muscarinic m_4 receptors are preferentially expressed in striatum, agonists are more potent to stimulate receptors linked to the phospholipase C pathway (McKinney, 1993), which normally are of the m_1 type. And fourth, even if the muscarinic m_4 receptor seems more expressed with in situ hybridization techniques (Vilaró et al., 1993; Brann et al., 1993), the muscarinic m_1 receptor is expressed in all spiny neurons, whereas the m_4 receptor is only expressed in 50% of them (Brann et al., 1993). With respect to the above observations, the response described was present in 94% of the neurons tested, AF DX 384 did not block the action of carbachol at higher concentrations, and phorbol esters mimicked carbachol effects, suggesting mediation by the phospholipase C pathway through protein kinase C activation. Therefore, although more detailed pharmacological analysis and more specific agonists and antagonists are needed to completely identify the class of receptor involved, the present data would favor the participation of muscarinic M_1 receptors.

The present experiments showed that the phospholipase C cascade may be involved in muscarinic actions (Góngora et al., 1988). This cascade generates diacylglycerol, an activator of protein kinase C, and phosphoinositides. The later compounds increase intracellular calcium (Berridge and Irvine, 1989). Intracellular calcium, then, might *increase*, not decrease, the afterhyperpolarizing potential commonly mediated at least in part by Ca^{2+}-activated K^+ conductances (Pineda et al., 1992, 1994). This is precisely the case in some cells (Jones et al., 1988; Sawada et al., 1989; Caulfield et al., 1993). However, a *reduction* in the afterhyperpolarization is found in neostriatal neurons in the presence of acetylcholine receptor agonists. In other neurons, postsynaptic protein kinase C activation has been implicated in the production of this same effect (Baraban et

al., 1985; Malenka et al., 1986; Sawada et al., 1989). And, in fact, PDB, a phorbol ester which activates protein kinase C, mimicked the cholinergic effects in neostriatal neurons. The effects might be specific because 30 μM 4α-PMA, a phorbol analog that does not activate protein kinase C, had no effect. In favor of this hypothesis is the fact that the amino acid sequence of a cloned Ca^{2+}-activated K^+ channel has the consensus sequence for protein kinase C-dependent phosphorylation (Atkinson et al., 1991).

A complication to the interpretation given above is that muscarinic receptors also mediate a decrease in the different Ca^{2+} currents known to be present (Bargas et al., 1994) in neostriatal neurons. Both muscarinic m_1 and m_4 receptors may be implicated (Howe and Surmeier, 1995). Therefore, this effect could also be mediated by protein kinase C (e.g., Doerner and Alger, 1992). Accordingly, part of the effect on the afterhyperpolarization could be mediated by a reduction in Ca^{2+} entry which would in turn cause a decrease in the Ca^{2+}-activated K^+ conductance that contributes to the afterpotential. Experiments are needed to clarify this point. However, experiments with other brain neurons have shown that a reduction in the Ca^{2+}-dependent afterpotential could be independent of the effects on the Ca^{2+} currents (e.g., Cole and Nicoll, 1984; Knöpfel et al., 1990; Washburn and Moises, 1992).

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