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Direct and indirect presynaptic control of dopamine release by excitatory amino acids

A. Chéramy, M. L'hirondel, G. Godeheu, F. Artaud, and **J. Glowinski**

Chaire de Neuropharmacologie, INSERM U 114, Collège de France, Paris, France

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Summary. Dopamine (DA) release from nerve terminals of the nigrostriatal DA neurons not only depends on the activity of nigral DA cells but also on presynaptic regulation. Glutamatergic neurons of cortical origin play a prominent role in these presynaptic regulations. The direct glutamatergic presynaptic control of DA release is mediated by N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole-4-propionate (AMPA) receptors, located on DA nerve terminals. In addition, by acting on striatal target cells, these glutamatergic neurons contribute also to indirect regulations of DA release involving several transmitters such as GABA, acetylcholine and neuropeptides. Diffusible messengers such as nitric oxide (NO) or arachidonic acid (AA) which are particularly formed under the stimulation of NMDA receptors may also participate to the regulation of DA release. In the present study, it will be shown that the co-application of NMDA and carbachol synergistically increases the release of [^{3}H]-DA and that this effect is reduced by mepacrine or 4-bromophenacylbromide (10^{-7}M), two inhibitors of PLA2. Therefore endogenously released AA induced by the co-stimulation of NMDA and cholinergic receptors seems to be involved, at least partly, in the release of DA.

Keywords: Excitatory amino acids – Dopamine release – Mouse striatal microdiscs – Presynaptic mechanisms – Diffusible messengers – Arachidonic acid

Introduction

Since the initial investigation of Giorguieff et al. (1977a) indicating that L-glutamate stimulates the release of [^{3}H]-dopamine ([^{3}H]-DA) from rat striatal slices, several *in vivo* and *in vitro* studies have been undertaken to further determine the mechanisms involved in this effect. Several approaches including animals implanted with push-pull cannulae (Chéramy et al., 1986; Leviel et al., 1990), microdialysis (Carter et al., 1988; Imperato et al., 1990; Keefe et al., 1992) and voltammetry (Suaud-Chagny et al., 1992) were used in studies performed *in vivo*. In most cases, striatal slices from the rat (Rudolph et al., 1983; Krebs et al.,

1994) and mesencephalic neuronal cultures (Mount et al., 1989) were used in experiments carried out *in vitro*. The direct presynaptic control of DA release by glutamate involves both AMPA and NMDA receptors located on nerve terminals of the nigrostriatal DA neurons. Glutamate also exerts indirect presynaptic regulations of DA release mediated by local circuits which involve the collaterals of medium sized GABAergic efferent neurons and striatal interneurons (Chéramy et al., 1991). In addition, studies performed in our laboratory have indicated that local circuits sensitive to NMDA and involved in the indirect presynaptic regulation of DA release are different in the two main compartments of the striatum: the striosomes and the matrix (Krebs et al., 1994). The presence of AMPA and NMDA receptors on DA nerve terminals and their contribution in a facilitatory presynaptic control of DA release was first suggested by studies performed in the presence of tetrodotoxin (Chéramy et al., 1986; Carter et al., 1988; Mount et al., 1989; Keefe et al., 1992). This was then confirmed using synaptosomes (Desce et al., 1991, 1992; Wang, 1991; Chéramy et al., 1996). Anatomical investigations have also provided direct evidence for the presence of AMPA and NMDA receptors on nigrostriatal DA neurons (Martin et al., 1993; Wüllner et al., 1993, 1994; Standaert et al., 1994).

The indirect presynaptic regulation of DA release resulting from the effects of glutamate or related agonists on striatal neurons was demonstrated using appropriate antagonists. For instance, both GABA and dynorphin which are released from collaterals of medium sized GABAergic neurons under the action of glutamate have been shown to inhibit the release of dopamine (Chéramy et al., 1986; Leviel et al., 1990; Krebs et al., 1994) and there is also evidence for a glutamatergic control of dopamine release mediated by cholinergic interneurons (Carter et al., 1988). In addition, to these classical indirect interactions, glutamate has been shown to increase the release of DA through the diffusible messenger nitric oxide (Hanbauer et al., 1992).

In the present article we will first review data obtained in our laboratory which indicate that transmitters other than glutamate itself such as acetylcholine can contribute to the regulation of the Mg^{++} block of NMDA receptors on DA nerve terminals. Then, we will describe more recent results indicating that endogenously formed arachidonic acid (AA) is also involved in a facilitatory control of DA release in the striatum.

Involvement of NMDA receptors in the control of [^{3}H]-DA release: cholinergic control of the magnesium block of NMDA receptors

In the absence of Mg^{++}, NMDA markedly enhances the release of [^{3}H]-DA (endogenously formed from [^{3}H]-tyrosine) from rat synaptosomes. However, in physiological conditions, i.e. in the presence of Mg^{++}, NMDA is without effect on [^{3}H]-DA release (Desce et al., 1992; Wang, 1991; Chéramy et al., 1996). This Mg^{++} block of the NMDA-evoked response can be eliminated by depolarisation or stimulation of AMPA receptors which are co-localised with NMDA receptors on DA nerve terminals (Desce et al., 1992).

As with glutamate, acetylcholine exerts a presynaptic facilitatory influence on [^{3}H]-DA release and both muscarinic and nicotinic receptors are involved

in this regulation first demonstrated on striatal slices (Giorguieff et al., 1977b) and then on striatal synaptosomes (Rapier et al., 1990; Chéramy et al., 1996). As for the activation of AMPA receptors, the stimulation of muscarinic and/or nicotinic presynaptic receptors facilitates the release of [^{3}H]-DA and allows the removal of the Mg^{++} block of NMDA receptors. The latter effect is mediated by the activation of a protein kinase C (Chéramy et al., 1996). In fact, according to different modalities, phosphorylated NMDA receptors seem to be less sensitive or insensitive to Mg^{++} (Chen and Huang, 1992).

Role of endogenous arachidonic acid

Experiments performed in our laboratory, on cultured striatal neurons from the mouse, have allowed us to show that acetylcholine or the mixed agonist carbachol, acting through M1 muscarinic receptors, potentiate markedly the glutamate or NMDA-evoked release of AA (Tencé et al., 1995). Protein kinase C was found to play a prominent role in the synergistic effects of NMDA and carbachol on the stimulation of AA release. Other experiments carried out on rat striatal synaptosomes revealed that exogenous AA markedly stimulates the release of [^{3}H]-DA, in a concentration- and Ca^{2+}-dependent manner. This effect was specifically reduced in the presence of inhibitors of protein kinase C (L'hirondel et al., 1996). These observations led us to verify whether endogenously released AA could be responsible, at least partly, for the important release of [^{3}H]-DA induced by the co-stimulation of NMDA and muscarinic

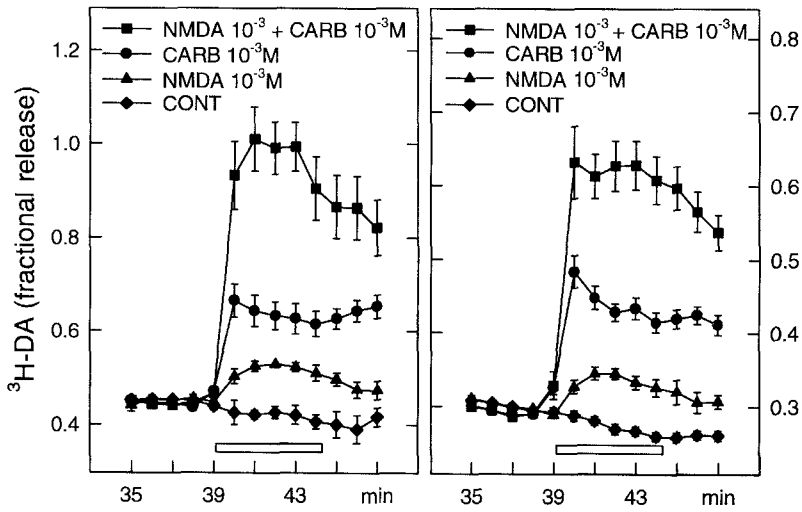

Fig. 1. Potentiation of NMDA-evoked release of [^{3}H]-DA by carbachol. Experiments were performed on rat (left panel) or mouse (right panel) striatal microdiscs prelabelled with [^{3}H]-DA, placed in superfusion chambers and superfused with an artificial CSF. NMDA and/or carbachol (*CARB*) were applied for 5 min (open rectangle). Means ± SEM of data obtained with 12 microdiscs in 3 independent experiments were calculated. In all groups, the evoked release was significantly higher than controls (*CONT*)

receptors. Therefore studies on the combined effects of NMDA and carbachol on the release of newly synthesised or taken up [^{3}H]-DA from microdiscs of tissues punched out in the striatum were performed in the absence or the presence of mepacrine. Since the potentiation by carbachol of the NMDA-evoked formation of AA was found to be more important in the mouse than in the rat, comparative release studies were carried out in both species.

In the presence of Mg^{++}, the combined effect of NMDA and carbachol was of higher amplitude than the sum of individual effects. However, no difference could be detected between the rat and the mouse (Fig. 1). In the absence of Mg^{++}, important synergistic stimulatory effects of carbachol and NMDA on the release of [^{3}H]-DA could be demonstrated in both species but this response was more important in the mouse than in the rat (data not shown). Both in the presence or absence of Mg^{++}, the amplitudes in the changes in [^{3}H]-DA release evoked by the co-application of NMDA and carbachol were found to be dependent on the concentration of each agonist, higher responses being found with increasing concentration of NMDA and/or carbachol (data not shown).

As particularly shown in the mouse, the stimulation of [^{3}H]-DA release induced by the combined application of NMDA and carbachol was markedly reduced (40%) in the presence of mepacrine even when the phospholipase A2 inhibitor was used at a low concentration (10^{-7}M) (Fig. 2) and this effect was also observed with another phospholipase A2 inhibitor, 4-bromophenacylbromide (10^{-7}M) (data not shown). Confirming the specificity of these effects, when used at 10^{-7}M, mepacrine was without effect on the basal efflux of [^{3}H]-DA and on the potassium (25 mM)-evoked release of [^{3}H]-DA. These observations suggest that endogenously formed AA is indeed involved in the control of [^{3}H]-DA release in the striatum.

Discussion

As demonstrated *in vivo*, glutamate may release DA even in the absence of nerve impulse flow in DA neurons (Chéramy et al., 1991). By acting on AMPA and NMDA receptors which are located on different striatal neuronal populations and afferent fibers, glutamate released from cortico- and thalamo-striatal fibres controls presynaptically the release of DA through various direct and indirect processes (Chéramy et al., 1991). By acting on striatal interneurons and efferent neurons, glutamate can stimulate local circuits contributing to the modulation of the direct glutamate-evoked release of DA. This is the case, for example, through the facilitation of cholinergic transmission (Chéramy et al., 1996). Finally, glutamate, through its action on somatostatin containing neurons, leads to the formation of nitric oxide which also stimulates the release of DA (Hanbauer et al., 1992). Similarly, we found that arachidonic acid, another diffusible messenger which is formed under the stimulation of AMPA, NMDA and glutamate metabotropic receptors, inhibits the uptake and stimulates the release of [^{3}H]-DA from striatal synaptosomes of the rat (L'hirondel et al., 1995). In addition, as demonstrated using inhibitors of phospholipase A2, glutamate and acetylcholine stimulate also the release of DA through their synergistic effects on the endogenous formation of arachi-

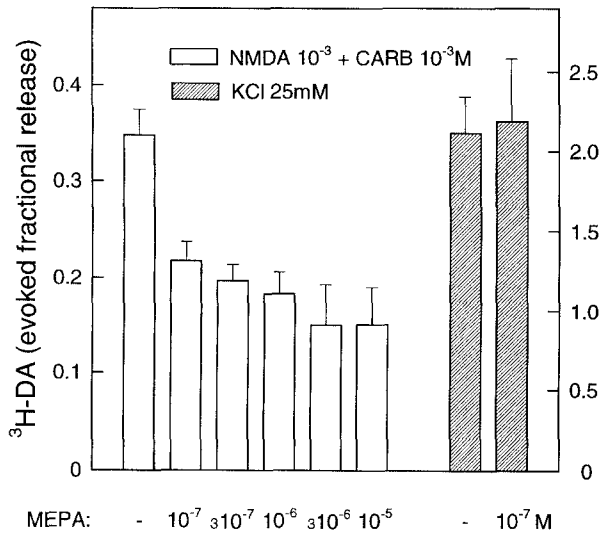

Fig. 2. Reduction by mepacrine of the NMDA plus carbachol evoked release of [^{3}H]-DA. Experiments were performed in the mouse, as indicated in Fig. 1, except that, when indicated, mepacrine (*MEPA*) was added in the CSF throughout the superfusion. KCl or NMDA + carbachol (*CARB*) were applied for 5 min and the average evoked release calculated. Means ± SEM of data obtained with 12 microdiscs in 3 independent experiments were calculated. In all groups, the evoked release was significantly higher than controls. Mepacrine significantly reduced the NMDA + carbachol, but not the KCl-evoked release of [^{3}H]-DA

donic acid. Therefore, cholinergic interneurons which are mainly innervated by neurons of thalamic origin could markedly amplify incoming signals delivered by corticostriatal glutamatergic neurons and the resulting formation of AA could also play a prominent role in the local control of DA release.

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Authors' address: Dr. A. Chéramy, INSERM U 114, Collège de France, 11 place Marcelin-Berthelot, F-75231 Paris Cedex 05, France.

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