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Brain Research 695 (1995) 1–9

BRAIN RESEARCH

Research report

Direct in vivo comparison of two mechanisms releasing dopamine in the rat striatum

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Accepted 23 May 1995

Abstract

A push–pull cannula supplied with artificial CSF was implanted in the striatum of anaesthetized rats, and the basal extracellular DA and DOPAC was assayed in the superfusates using HPLC and electrochemical detection. Simultaneously, a carbon fibre electrode was implanted in close proximity of the cannula and the evoked DA release was detected by differential pulse amperometry during stimulation of the DA axons. Local treatments with cadmium (100 μM) blocked the evoked DA release (−90%), but substantially increased the basal extracellular DA (+125%). The effects of glutamate agonists NMDA (1 mM) and kainate (0.1 mM), known to increase basal extracellular DA were confirmed (+150% and +60% respectively). It was, however, simultaneously observed that the evoked DA release was inhibited (−80% and −50%, respectively). Amphetamine (1 μM) released DA (+150%) and produced also an increase (+100%) of the evoked DA release. These results, apparently conflicting, show that the two mechanisms releasing dopamine (firing-dependent and not) can be directly and simutaneously observed. These two releasing processes appear to be not strictly antagonist. They are also differently and independently modulated by calcium and by local influences such those conveyed by glutamate.

Keywords: Dopamine-release; Cadmium; Striatum; NMDA; Kainate; Amperometry, in vivo; Superfusion, in vivo; Rat

1. Introduction

It was shown that extracellular dopamine in the striatum can result from a calcium-dependent process of release, triggered by the DA cell firing. Indeed, a close relationship between DA release and electrical stimulations of DA axons was clearly established using amperometrical techniques, with a locally-implanted carbon-fibre electrode, or dialysis techniques [12,17,47]. The extracellular DA concentration in the caudate nucleus could however be also relevant to something other than the electrical activity of dopaminergic cells. An increased DA release was even observed in the striatum under experimental conditions decreasing cell firing in the substantia nigra [43]. Since the first proposal by Raiteri et al. [41] that DA could be released by a calcium-independent and carrier-mediated process, numerous reports have claimed that the firing-dependent DA release does not explain all the reported alterations of the extracellular DA concentration and that an additional releasing process should occur [27,33,40,48]. Recently, Grace [19] gathered these data and proposed the presence of a 'tonic' release of the amine in the striatum mainly dependent on direct influences on the DA terminals.

The physiological significance of two mechanisms of DA release in the striatum has to date remained unclear, mainly because their respective contribution to the extracellular DA was difficult to establish. In an attempt to discriminate between these two mechanisms of release we measured, in vivo, the extracellular DA by the use of a push–pull cannula during the superfusion of substances known to alter the amine release. Simultaneously, during these treatments and using differential pulse amperometry (DPA), we evaluated the ability for the DA terminals to release DA in response to axonal stimulations.

An application of cadmium ions was first tested to validate the method. Indeed only the evoked DA release is known to be dependent on the calcium influx. Two additional treatments, reported to preferentially affect the calcium-independent DA release were also tested: NMDA [26,34] and amphetamine [24,35]. The effects of these treatments were observed on both the basal extracellular

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SSDI 0006-8993(95)00706-7

DA and the stimulation-evoked DA release. By the use of these treatments already proposed to be specific of one or the other of the two DA-releasing mechanisms, we attempted to differentiate them.

2. Material and methods

Wistar male rats weighing about 300 g (Iffa Credo, France) were used in this study. Anaesthesia was induced by i.p. injection of chloral hydrate (400 mg/kg) and maintained by continuous i.p. perfusion with the same substance (50 mg/ml, 1 ml per hour). The animals were implanted simultaneously with (i) a push–pull cannula in the head of the caudate nucleus, (ii) a carbon fibre electrode in close proximity of the cannula tip and (iii) a bipolar electrode in the medial forebrain bundle (MFB, Fig. 1). The stereotaxic contention was realised with a David Kopf stand, the coordinates being from the Atlas of Albe-Fessard et al. [1]. The following substances were used: NMDA and GBR12909 (RBI, USA), sulpiride and bicuculline (Sigma, France), kainate (Tocris Neuramin, UK) and amphetamine (Cooper, France).

2.1. Superfusion procedure

The alterations of the basal extracellular DA were evaluated using a local superfusion with a push–pull cannula. Rats were implanted with a push–pull cannula lowered vertically in the head of the caudate nucleus (A: 8.2; L: 3; H: 6.5 in mm). The cannula was supplied (12 μl/min) with an artificial cerebrospinal fluid the composition of which has already been detailed [37]. Samples (240 μl) were collected every 20 min and 10 μl of a protective medium (1 M phosphoric acid added with 0.1% EDTA and 0.2% $Na_2S_2O_5$) were added. Superfusion started immediately after the cannula implantation; nevertheless, during the first hour the perfusion fluid was not collected. The collected samples were analysed by high-pressure liquid chromatography and electrochemical detection as described elsewhere [31]. The range of the DA amounts in superfusates was between 20 and 40 pg by 20 min fractions. Prior to any pharmacological treatment a resting period of 80 min was observed, and the mean of the four samples collected during this period of time was considered as representative of the basal extracellular DA concentration (100%). All the fractions were then recalculated as a function of this mean and expressed as a percent of the so called 'spontaneous release'.

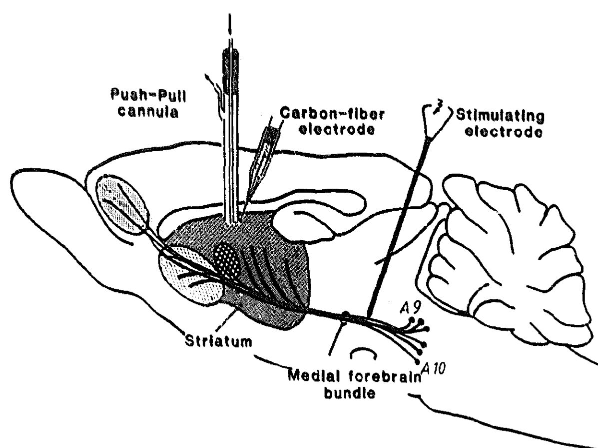

Fig. 1. Diagram of the experimental design allowing simultaneous detection of the two types of DA releasing process. A push–pull cannula was implanted vertically in the caudate nucleus of anesthetized rats and supplied with an artificial cerebrospinal fluid in which dopamine was detected by electrochemical detection after HPLC analysis. A carbon fibre electrode was lowered following an oblique axis to obtain a distance of about 300 μm between the tips of the two probes. Differential pulse amperometry allowed the detection of the DA released during stimulation of the ascending dopamine fibres with a stimulatory electrode implanted in the lateral hypothamus.

2.2. Amperometrical procedures

The ability of DA terminals to release DA in response to axonal stimulation was evaluated by differential pulse amperometry. Carbon-fibre electrodes were produced and treated following the methods described by Gonon et al. [18]. Prior to their implantation carbon-fibre electrodes were calibrated in vitro in a 50 mM phosphate-buffered saline solution containing 50 nM DA and 100 μM ascorbic acid. The value of the potential corresponding to the oxidation of DA was determined in vitro with differential normal pulse voltametry (DNPV) using a pulse voltametric system ('Biopulse', SOLEA Tacussel ®, France) and following the method described by Gonon and Buda [17].

The skull and dura-mater were opened and the pia-mater was carefully removed under binocular lens. The carbon-fibre electrode was implanted following an oblique axis with a view to being as close as possible to the tip of the push–pull cannula (from 0.2 to 0.5 mm) and lowered between 3.0 and 3.5 mm from the cortical surface. The Ag/AgCl reference was a silver wire (0.5 mm) coated with AgCl by electrolytic treatment and maintained in contact with the skull by means of a liquid junction. The bar ear was used as auxiliary electrode. After the electrode had been implanted in the striatum, differential pulse amperometry DPA was used as described by Gonon [16] with the carbon-fibre set to the potential previously determined by DNPV (about 80 mV). The differential oxidation current was monitored every second.

In addition, a bipolar electrode was implanted in the MFB containing the DA ascending fibres (coordinates: A: 5; L: 1.3; Ht :2). Every 4 min, MFB was stimulated for 20 s by 20 bursts (one per second) of 25 positive square pulses, 0.5 ms each, with 25 ms interpulse (40 Hz theoretical frequency). Each burst was triggered 300 ms after the DPA measurement.

All the pharmacological treatments were applied by addition to the fluid supplying the cannula. Glutamate

(GLU) agonists NMDA and kainate were added to various concentrations (10 nM to 1 mM); only the effects obtained with 1 mM NMDA and 0.1 mM kainate are presented here. Due to the sensitivity of the NMDA receptor to Mg^{2+} ions, the experiments devoted to testing the effects of NMDA were realized with a superfusing fluid in which Mg^{2+} ions were omitted and replaced by 0.83 mM Ca^{2+} ions. The cadmium ions were added to the superfusing fluid at a concentration of 100 μM in the presence of 1.1 mM calcium ions and amphetamine at a concentration of 1 μM. At the end of the experiment, carbon-fibre electrodes were recalibrated in vitro to detect a possible modification of the oxidation potential for DA. Finally, after deep anaesthesia, animals were submitted to an intracardiac perfusion with formaldehyde (4%) to allow a further histological verification of the stimulating-electrode and cannula locations.

3. Results

3.1. The evoked DA release

In the present study, DPA was used to detect evoked-DA release and no attempt was made to evaluate DA extracellular amount with this technique. Each 20 s stimulation train produced a large increase of the amperometric signal in the ipsilateral caudate nucleus strictly restricted to the stimulation period (Fig. 2). The amplitude of the peaks occurring was roughly constant over time. The four responses obtained prior to the treatment were averaged and considered as the control response (100%). As discussed elsewhere by Gonon [16] and Suaud-Chagny et al. [46], the increase of the oxidation current under these conditions is likely to be due mainly to the DA released in spite of the fact that a part could be due to DOPAC that is not differentiated by the carbon-fibre electrode. Supporting this hypothesis is the fact that the response to MFB stimulation is increased to about 300% after an i.p. pargyline injection (75 mg/kg), a blocker of the monoamine oxidase enzyme (data not shown).

Under our experimental conditions, the MFB stimulation altered the differential oxidation current but remained ineffective on the amount of basal extracellular DA (Fig. 2). The MFB stimulation lasted only 0.06% of the collection time (25 pulses per second and 4 periods of 20 s every 20 min). Thus, lasting such a short period of time, an increased release of the amine remained undetectable in the superfusing fluid.

3.2. The superfusion in the presence of cadmium ions

To block the voltage-dependent calcium channel, 100 μM cadmium was added to the artificial LCR supplying the cannula. This treatment resulted in the disappearance of the stimulation-evoked release of DA detected with DPA (Fig. 3). The same effect could be obtained with 1 mM cobalt in place of cadmium and was unchanged in the presence of 0.5 μM GBR12909 (data not shown). Surprisingly, the amount of DA detected in the superfusing fluid during the same treatment followed a different response curve (Fig. 3). In fact, the amount of the collected amine was initially increased during the first 40 min of application. Over this period of time, the DA collected fell below control values. In the presence of 0.5 μM GBR12909 simultaneously added with cadmium, no further increase in

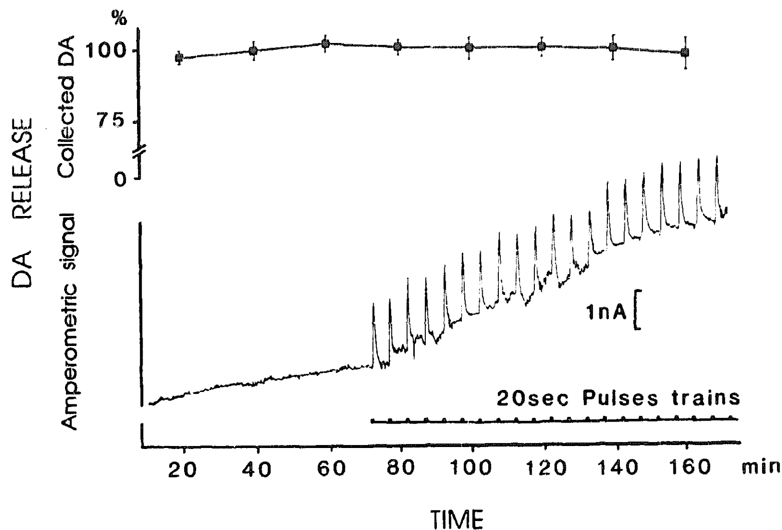

Fig. 2. Top: collected DA in successive 20 min fractions. The values (20–40 pg) of the three first fractions collected were averaged and used to determine the spontaneous release (100%). All fractions were then recalculated as a percentage of this mean and averaged (±S.E.M.) with the corresponding fraction of six other animals. Bottom: amperometric signal (sampling = 1 s), obtained on a single animal, from the carbon-fibre electrode before and during the successive 20 s stimulations every 4 min. Each stimulatory pulse train applied to the MFB induced an increase of the oxidation peak restricted to the stimulatory period (the evoked DA release). Due to the long duration of the superfusates collection (20 min), the MFB stimulation remained without effect on the amount of DA collected by the means of the cannula.

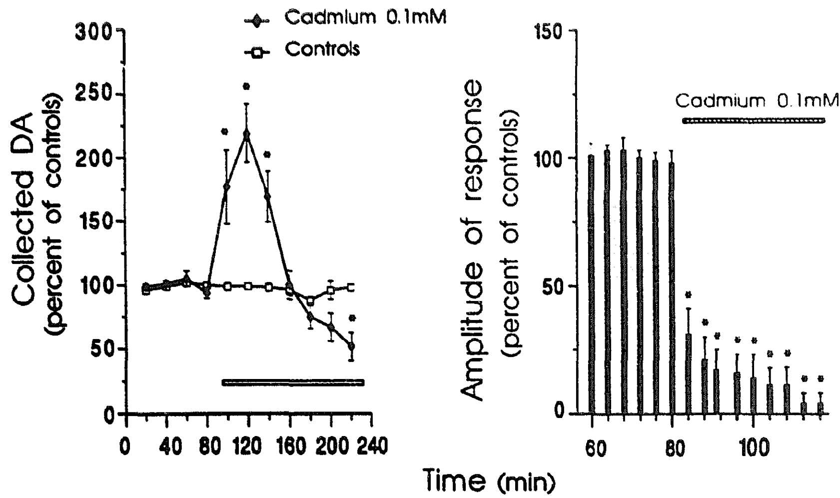

Fig. 3. Effect of a local persistent superfusion with 100 μM cadmium ions, in the presence of a no mal concentration of calcium, on the spontaneous and the stimulation-evoked DA release. Cadmium treatment increased the DA collected through the cannula (left) but reduced the stimulation-evoked DA release (right). The control values (100%) are the mean of the values obtained during the pretreatment period. Each value is the mean ±S.E.M of corresponding measures obtained from 6 control and 6 treated animals. * $P < 0.05$.

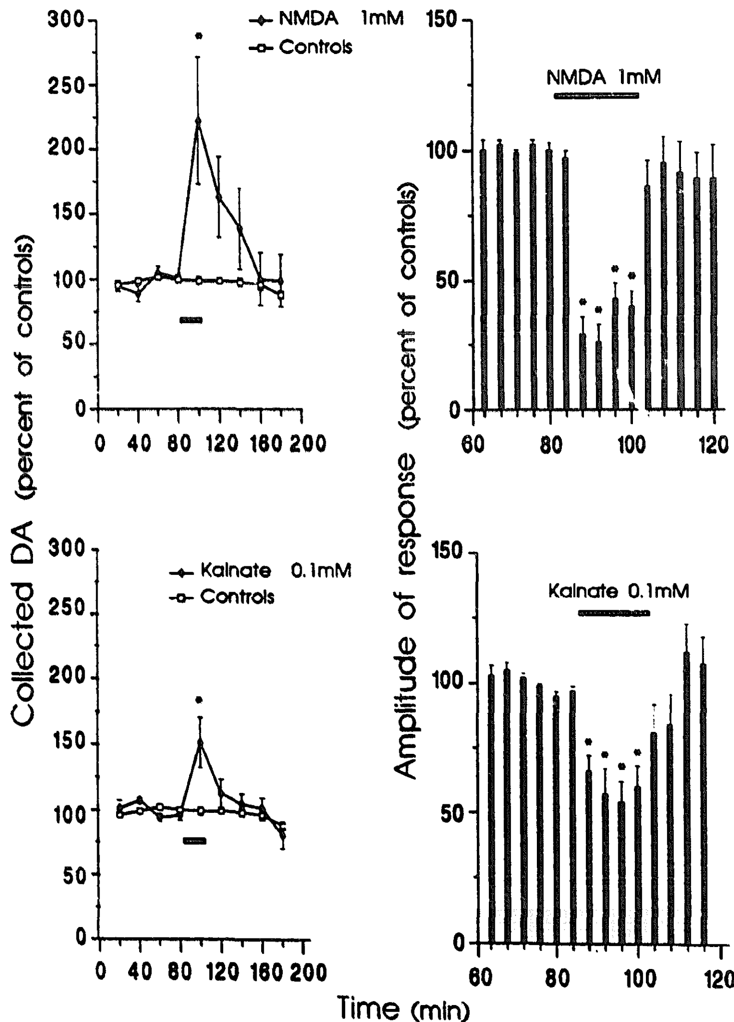

Fig. 4. Local applications (20 min) of 1 mM NMDA and 0.1 mM kainate increase the amount of DA collected through the cannula (DA release) but decrease the stimulation-evoked DA release (evoked DA release). Left: amounts of DA collected through the cannula during a local application of 1 mM NMDA (up) and 0.1 mM kainate (down). Right: decreased amplitude of amperometric signal evoked by the MFB stimulation during the same treatments. $n = 6$, $P < 0.05$.

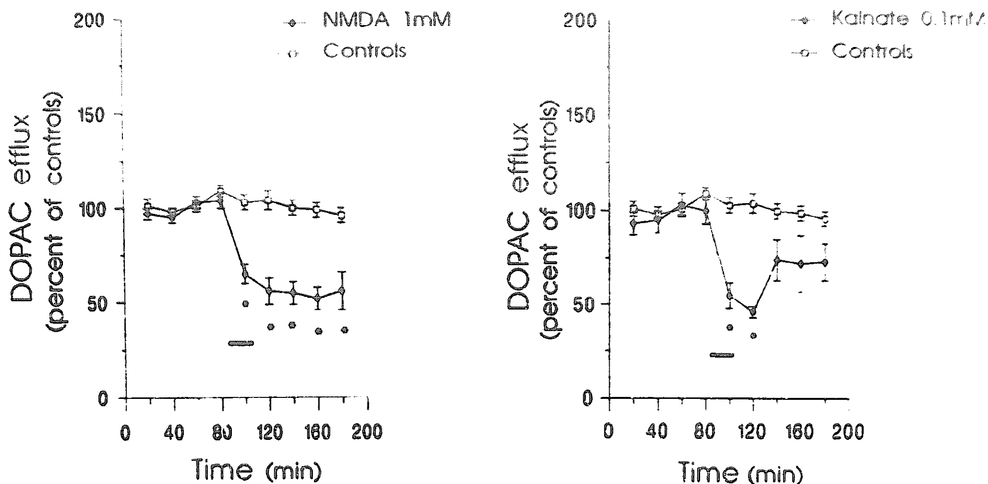

Fig. 5. Decrease of the DOPAC amounts in the superfusing fluid during the local application (20 min) of 1 mM NMDA (left) and 0.1 mM kainate (right). The control values (100%) are the mean of the values obtained during the pretreatment period. Each value is the mean ± S.E. of corresponding fractions obtained from 6 control and 6 treated animals. *: $P < 0.05$.

the amount of DA in the superfusing fluid could be detected (Fig. 6).

3.3. Local superfusion with GLU agonists

The GLU agonists NMDA (1 mM) and kainate (0.1 mM) added to the superfusing fluid increased the amount of DA collected through the push–pull cannula (Fig. 4) and reduced the DOPAC efflux (Fig. 5). These effects disappeared in the presence of 0.5 μM GBR12909, a DA carrier blocker (Fig. 6). In contrast, the same treatments reduced the amperometric signal evoked by MFB stimulation (Fig. 4) and were not counteracted by the presence of 0.5 μM GBR12909. To determine whether the effects of the GLU agonists on the stimulation-evoked DA release could be indirect, 1 mM sulpiride (a D2 receptor antagonist) or 1 mM bicuculline (a $GABA_B$ receptor antagonist) were simultaneously perfused through the cannula, but they did not counteract the observed inhibition.

Very low doses of GLU (10 nM) were described as affecting the DA release. In the present case, lower doses of NMDA and kainate (from to 10 nM to 10 μM) remained without effect either on the spontaneous release detected in the superfusing fluid or on the stimulation-evoked DA release.

3.4. Local superfusion with amphetamine

Amphetamine (1 μM) was added during 20 min to the superfusing fluid. During this treatment (Fig. 7) the amount

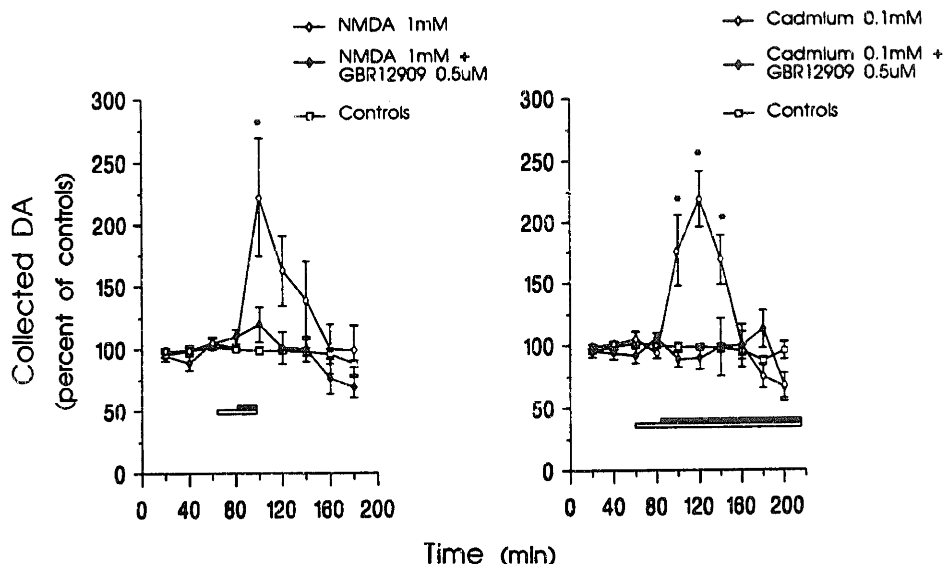

Fig. 6. Blockade of the effect of cadmium and NMDA by a co-superfusion of GBR 12909 (0.5 μM). Experimental design and presentation of results are the same as in Fig. 3. $n = 6$, $P < 0.05$.

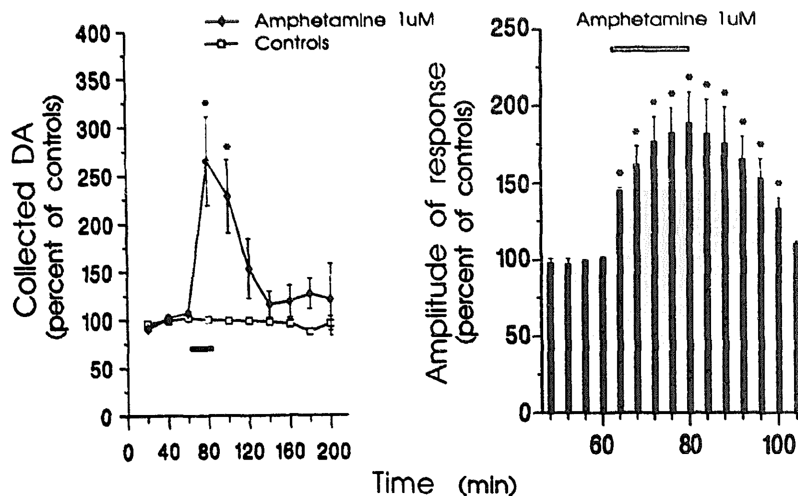

Fig. 7. Amphetamine (1 μM) added to superfusing fluid for 20 min increased both the spontaneous (left) and the stimulation-evoked DA release (right). Experimental conditions and presentation of results are as described in Figs. 2, 3 and 4. $n = 5$, * $P < 0.05$.

of DA collected was enhanced (250%) and the stimulation-evoked DA release was increased (300%). With this dose of amphetamine, the parameters measured returned to the control values soon after the cessation of the treatment.

4. Discussion

In the present study, it was observed that local treatments within the rat striatum including NMDA, kainate, cadmium and amphetamine, can affect in different ways the stimulation-evoked DA release as observed by DPA, and the basal extracellular DA collected through a push–pull cannula. These discrepancies suggest that, in the experimental conditions used, superfusion and DPA were relevant to different molecular mechanisms evoked by the pharmacological treatments. In a recent study [32] it was evidenced that calcium dependency is not a valid criterion to discriminate between the various mechanisms releasing DA. Indeed, other steps of the DA metabolism (synthesis, storage) are dependent on the availability of calcium ions and greatly interfere with DA release.

4.1. Evoked DA release

It is not surprising that cadmium, an agent blocking calcium channels, interrupted the firing-dependent DA release and many authors reported such an effect of cadmium on the DA release evoked by various agents [3,5]. When locally applied, 1 mM NMDA also blocked the evoked DA release. This effect, already reported by others [13], was presumably due to a direct action of NMDA or kainate on DA terminals. Indeed, an indirect effect of GLU agonists through extracellular DA or GABA could not explain our results, since neither sulpiride nor bicuculline was able to counteract this NMDA effect. The mechanism of this reversible action of NMDA could be similar to the 'depolarization block' observed at the cellular level [6,20]. In contrast to GLU agonists and cadmium, amphetamine appeared to activate the evoked DA release. This substance was already described as potentiating the impulse-dependent DA release [17,46,49]. However, that amphetamine really increases the evoked DA release is unlikely, since the action of amphetamine was often described as independent of calcium ions. Moreover, it was shown that, on striatal slices, amphetamine inhibits electrically evoked [^{3}H]DA release [25]. The slight increase we observed here could thus be also due to a well-known inhibition of the DA reuptake [15,22].

4.2. Extracellular DA

In contrast to the effects observed on the evoked DA release, the extracellular DA was largely enhanced during the application of cadmium, NMDA, kainate and amphetamine. The increased extracellular DA during the first hour of cadmium application is not simple to explain. However, in the literature also the effect of cadmium is controversial, since either a reduction [51] or no change [5] in basal extracellular DA was reported after cadmium application. Furthermore, the same uncertainty about the cadmium action comes from observations on other transmittory systems [21,36,38]. The biphasic effect we observed (a decrease following an increase) could explain these conflicting results. Any way, the ability of GBR12909 to block the effect of cadmium suggests that the DA carrier protein may be involved. The present effect of cadmium is to some extent paradoxical, since a superfusion with a calcium-free medium is well known to reduce the basal extracellular DA [28,32,39,50]. This ambiguity was addressed in a recent study [32] in which a dramatic reduction of the DA synthesis was observed that could be responsible for the reduced release. In addition, cadmium

have also been shown to inhibit the Na^+/K^+ ATPase [7,42] that could result in an alteration of the sodium gradient responsible for the exhaustion of DA by a transport mechanism. Cadmium could thus exert its own action in addition to the blockade of calcium channel. Concerning the Glu agonists, our results are in agreement with numerous reports about a DA-releasing effect of NMDA. The blockade of this NMDA-enhanced DA release by GBR12909 ascertained that it concerns only a carrier-dependent DA-releasing process, as already proposed by Lonart and Zigmond [34] and by Keefe et al. [26]. In line with the effects of GLU agonists and cadmium, amphetamine increased the extracellular DA. The effect of this substance is well known to be independent of the presence of calcium in the extracellular space, leading to the concept that amphetamine releases DA independently of the firing of the DA cells [44]. In addition, the carrier-mediated DA release is likely to be involved in the amphetamine action since nomifensine, an uptake blocker, has been shown to block the releasing effect of this substance [23].

4.3. Intraterminal DA

The effects of all these treatments on the intraterminal DA can also be questioned, since cytosolic DA could interfere with the carrier-mediated release of DA. Indeed, as proposed by Levi and Raiteri [29], an increased cytosolic DA due to an increased synthesis or a displacement of granular stores could lead to an increased availability of DA for the carrier-mediated release. It was proposed that DA synthesis is enhanced in the presence of low doses of GLU (10 nM) and is reduced by higher ones [31]. Alterations of the DA synthesis by GLU and agonists were later observed by other groups [2,8,10]. However, Desce et al. [10] reported an increase of the DA release simultaneously with a decrease of the DA synthesis on a synaptosomal preparation incubated in the presence of NMDA. In agreement with this last observation, in our experiments, NMDA (Fig. 5) as cadmium [32] reduced the DOPAC efflux that can indicate a reduced cytosolic DA pool from which DOPAC is directly coming [45,52]. It can thus be proposed that NMDA, kainate and cadmium activate the carrier-dependent DA release directly, probably through an alteration of the sodium gradient rather than through an overloading of the terminal with DA resulting from a vesicular displacement of the amine or an increased synthesis. At the dose we used (1 μM), amphetamine activated the DOPAC efflux [30], indicating that under these conditions the monoamine oxidase was not inhibited and suggesting an increase of the cytosolic DA. Furthermore, amphetamine is known to enhance the DA synthesis [9,14] and was proposed to displace the stored DA from the vesicles [4,11]. The enhanced carrier-mediated release can thus be explained by the means of an overloading of DA terminal with the amine.

Whatever the mechanism involved, it is clear that extracellular DA is dependent in vivo on both the firing activity and a carrier mechanism proposed quite a long time ago. The simultaneous use of push–pull superfusion and voltammetry will thus allow us to differentiate these and to investigate the respective contribution of these two transmittory modes to the dopaminergic function in the striatum.

5. Conclusion

These results constitute, to our knowledge, the first direct observation in vivo of the two DA-releasing mechanisms. This observation allowed us to compare the two processes responsible for DA neurotransmission in the striatum and to show they are independently regulated. They also confirm that GLU probably favours the firing-independent mechanism by a direct action on the amine transport. These observations lead one to reconsider many of the previous observations about DA release, taking into account which of the two mechanisms is involved.

Acknowledgements

This study was supported by DRET (No. 92157) and COFAG.

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