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Research report

Differential recruitment of N-, P- and Q-type voltage-operated calcium channels in striatal dopamine release evoked by 'regular' and 'burst' firing

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Abstract

This study used the peptides ω-conotoxin GVIA, ω-agatoxin IVA and ω-conotoxin MVIIC, singly and in combination, to investigate the relative involvement of N-, P- and Q-type voltage-operated calcium channels in the control of striatal dopamine release. Electrically stimulated dopamine release was measured by fast cyclic voltammetry at carbon fibre microelectrodes in rat striatal slices. The contribution of these channel subtypes was compared in dorsolateral and medial neostriatum for 'regular' (discrete) and 'burst' stimulation modalities. In dorsolateral neostriatum, a role for N-, P- and Q-type channels was demonstrated for discrete stimulations, whilst at least one other unidentified channel was also involved in dopamine release on 'burst' stimulations. Similarly, in the medial axis of the neostriatum, N-, P- and Q-type channels were involved in dopamine release for discrete stimulations, and N-, Q- and at least one other channel type for 'burst' stimulations. However, blockade of P-type channels had no effect on dopamine release for 'burst' stimulations in the medial axis. In both regions and stimulation paradigms, N-type channels played a greater role than P/Q-type channels. In the medial axis of the neostriatum there was a smaller contribution by N- and P-type channels and the unidentified component, but a greater Q-type contribution to DA release. 'Burst' stimulations induced a lesser involvement of N- and P-type channels than discrete stimulations, and a greater role of the unidentified component. In summary, this study suggests that there is heterogeneity in the distribution of functional voltage-operated calcium channel subtypes in the neostriatum, and differences in subtype recruitment for different firing patterns.

Theme: Excitable membranes and synaptic transmission

Topic: Calcium channel structure, function and expression

Keywords: Voltage-operated calcium channel; Dopamine; Neostriatum; Patterned firing; Fast cyclic voltammetry; Brain slice

1. Introduction

Chemical neurotransmission occurs by exocytosis of synaptic vesicles, triggered by a rise in cytosolic calcium, to expel transmitters into the extracellular compartment [17]. Under physiological conditions in neurones, this is achieved by entry of extracellular calcium through membrane-bound voltage-operated calcium channels (VOCCs), activated when an action potential invades a neurotransmitter release site.

VOCCs are subdivided based on their biophysical and pharmacological properties [2]. At present L-, N-, P-, Q-, R- and T-type channels have all been characterised, and O-type channels [1] have also been proposed.

T-type channels are activated at potentials between −65 and −50 mV, show voltage-dependent inactivation during maintained depolarisation and deactivate relatively slowly upon repolarisation [31]. Conversely, L-, N-, P-, Q- and R-type channels are all activated at approximately −20 mV. They differ in their pharmacology and their kinetics of inactivation during both maintained depolarisation and deactivation after repolarisation: R-type channels are the

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fastest to deactivate, followed in order by Q-, N-, L- and P-type channels.

In the past decade or so, the principal advances in the pharmacology of VOCC subtypes have come through the purification and characterisation of peptide toxins from invertebrate venoms. In particular, peptides from the predatory marine snails, *Conus geographus* and *Conus magus* (conotoxins) and the funnel web spider, *Agelenopsis aperta* (agatoxins) have shown specificity for VOCC subtypes [21].

Previous studies have addressed the involvement of voltage-operated calcium channel subtypes in dopamine (DA) release in the neostriatum (CPu). Typically, DA release was evoked by high concentrations of potassium [14,18] or long electrical trains [8,14]. Some of these studies also relied on measurement of [^{3}H]-DA [8,32]. With the use of real-time electrochemistry, endogenous DA can be measured on-line for relatively subtle electrical stimulations, and recordings can be carried out in discrete anatomical subregions of the CPu [27,28].

The different high-voltage-activated VOCC subtypes differ in their deactivation kinetics, but the necessity for multiple subtypes controlling neurotransmitter release is rarely addressed. A possible role for this diversity could be to allow processing of patterned firing activity. Dopaminergic neurones are known to exhibit patterns of 'regular' and high frequency 'burst' firing [22] whereby action potentials are generated either singly or in bursts of up to 20 [9]. Thus, in this study, the effect of VOCC antagonists on DA efflux for discrete single-pulse electrical stimulations and 20-pulse high frequency trains were compared. Single-pulse stimulations were considered to equate to 'regular' neuronal firing, whereas 20-pulse stimulations approximate 'bursts' of electrical activity.

Several groups have also described regional heterogeneity of striatal DA release [5,16,23], where DA release on 'burst' stimulation is smallest in dorsolateral CPu, and greatest along the medial axis of the CPu. In part, it is thought that these differences may be a reflection of the different dopaminergic afferents to the two regions: unlike the dorsolateral quadrant of the striatum whose input is almost solely from the A9 cell group, the medial axis of the neostriatum is also innervated by the ventral tegmental area (A10) [10]. This study investigated the effects of VOCC antagonists on DA release in these two striatal regions to test whether these differences could be implemented through the use of different VOCC subtypes.

2. Materials and methods

2.1. Brain slices

Male Wistar rats (150–200 g) were sacrificed by cervical dislocation and a block of brain containing the CPu was rapidly removed and chilled in ice-cold, pre-oxygenated artificial cerebrospinal fluid (aCSF) at −1 to +1°C. The block was then sectioned into 350-μm-thick coronal slices on a Vibratome (752M Vibroslice, Campden Instruments Ltd, Leicestershire, UK). Slices were transferred to a holding chamber containing aCSF at room temperature, bubbled with 95% O_2/5% CO_2 until needed. The slices were allowed to equilibrate in the recording chamber for at least 30 min before the first stimulation was applied. In the recording chamber, the slice was superfused at 1 ml/min with 32°C aCSF throughout the experiment.

Artificial CSF was composed of 124 mM NaCl, 2 mM KCl, 1.25 mM KH_2PO_4, 2 mM $MgSO_4.7H_2O$, 25 mM $NaHCO_3$, 2 mM $CaCl_2.6H_2O$, 11 mM D-glucose, and was oxygenated with 95% O_2/5% CO_2 for 1 h prior to its use.

2.2. Electrochemistry

DA efflux was measured by fast cyclic voltammetry (FCV) at carbon fibre (7 μm diameter×~50 μm in length) recording electrodes [3] using a dual channel potentiostat (Millar Dual Voltammetric Analyser, PD Systems Ltd, Surrey, UK). This allowed recordings to be made simultaneously at two sites in the brain slice, one in the most dorsolateral part of the CPu and one along its medial axis (adjacent to the lateral ventricle). At each site, there was a separate recording and stimulating electrode. Both recording electrodes were connected to the headstage of the potentiostat, receiving input waveforms from a single waveform generator while producing independent outputs.

Recording electrodes were positioned between the tips of the bipolar stimulating electrodes, penetrating the brain slice by about 80 μm. Reference (Ag/AgCl cylinder; Clark Electromedical Instruments, Berkshire, UK) and auxiliary (500-μm-diameter stainless steel wire) electrodes were submerged in the superfusant at a convenient location in the recording chamber.

The input voltage (1.5 cycles of a triangle waveform, −1.0 to +1.4 V vs. Ag/AgCl, 480 V/s) was applied to the recording electrode every 500 ms. Current signals prior to a stimulation were subtracted from those obtained following the stimulus to eliminate charging current and yield the Faradaic current due to DA oxidation and subsequent reduction. The output of a sample-and-hold circuit, monitoring the current at the oxidation potential for DA (approximately +600 mV vs. Ag/AgCl), was recorded on a strip chart recorder (PL4, Lloyd Instruments, Hampshire, UK).

2.3. Electrical stimulation

DA release was evoked by electrical pulses (100 μs, 10 mA) across tungsten bipolar electrodes (500 μm tip separation; A-M Systems Inc, Carlsborg, WA). These stimulations are believed to each elicit an endogenous action potential by activation of voltage-operated sodium channels, since the evoked DA release is abolished in the

presence of tetrodotoxin (data not shown). Stimulations were generated by a single stimulator unit whose output was conveyed via two pulse buffers and stimulus isolators (Digitimer Ltd, Hertfordshire, UK) to allow simultaneous delivery of stimulus pulses in each striatal region. Single- (1p) and 20-pulse (50 Hz; 20p) stimulations were applied alternatively every 4 min. 1p stimulations were used to mimic regular neuronal firing, whereas 20p stimulations were used to model burst firing.

2.4. Toxins

ω-Conotoxin GVIA, ω-agatoxin IVA and ω-conotoxin MVIIC were applied to the brain slice at concentrations based largely on current literature [20,24] and personal communication [A. Randall, 1998]. 100 nM ω-conotoxin GVIA was used to block N-type channels selectively. ω-Agatoxin IVA was used at 15 nM to block P-type channels selectively and, at 200 nM, to block both P- and Q-type channels. N- and P-type channels were blocked simultaneously by concurrent application of ω-conotoxin GVIA (100 nM) and ω-agatoxin IVA (15 nM). The combination of ω-conotoxin GVIA (100 nM), ω-agatoxin IVA (15 nM) and ω-conotoxin MVIIC (500 nM) was used to block N-, P- and Q-type channels. Stock solutions of the toxins were made up in deionised water and subsequently diluted in aCSF. Following three stable stimulation pairs, treatments were applied via the superfusant for 96 min (12 stimulation pairs) except for 200 nM ω-agatoxin IVA, which was only applied for 48 min.

ω-Agatoxin IVA was a kind gift from Pfizer Research Inc (Groton, CT). ω-Conotoxin GVIA and ω-conotoxin MVIIC were purchased from Bachem AG (Bubendorf, Switzerland).

2.5. Statistical analysis

The effects of the toxins on DA efflux were assessed for three stimulations after 28 to 48 min exposure to the treatment. Differences between treatment groups (and controls) were examined using one-way analysis of variance (ANOVA) with post-hoc evaluation by Newman–Keuls Multiple Comparison Test. Regional differences in toxin effects were examined with unpaired *t*-tests, and effects for different stimulation paradigms were compared by paired *t*-test (effects on DA efflux for 1p stimulations were paired with those for 20p at the same recording site).

3. Results

Electrical stimulation of the striatum with single pulses or trains consistently evoked DA efflux that was measurable by FCV (Fig. 1) and stable on successive stimuli, in the absence of pharmacological intervention. In dorsolateral CPu, 1p stimulations evoked a transient change in extracellular DA concentration with a peak approximately 100 nM above the baseline. The response to 20p stimulations was a signal with a mean peak concentration of about 1.5 times that of 1p. In the medial axis of the CPu, 1p stimulations evoked a slightly smaller peak than in dorsolateral CPu (~70 nM) and 20p evoked a signal with a mean peak of 7.3 times that of 1p. This was similar to the responses observed by Davidson and Stamford [5]. Administration of VOCC blockers generally decreased DA release. Fig. 2 shows the development of the effects of each of the treatments with time. Toxin effects on DA efflux reached a plateau within 28 min in most cases. In dorsolateral CPu, the effect of 15 nM ω-agatoxin IVA did not appear to completely level off within the time-course of the experiment. However, the period during which it was assessed was beyond the steepest part of its curve.

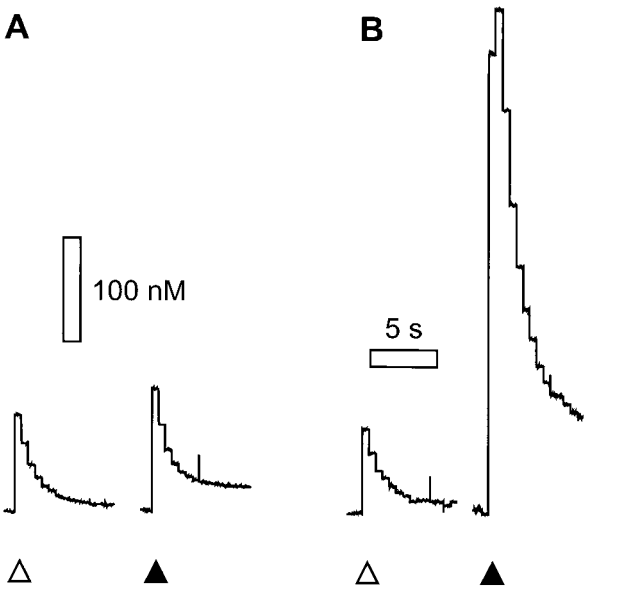

Fig. 1. Representative raw traces of fast cyclic voltammetry recordings of DA release following 1p and 20p electrical stimulations in the (A) dorsolateral and (B) medial axis of the CPu. 1p stimulations are represented by open and 20p stimulations by filled triangles. The scale bars represent DA concentration and time for each trace.

3.1. Single-pulse stimulations ('regular' firing)

All treatments significantly reduced DA efflux for 1p in the dorsolateral CPu (all $P<0.001$ vs. control; Fig. 3, left panel). ω-Conotoxin GVIA abolished DA efflux within 36 min when applied alone or with other toxins. 15 nM ω-agatoxin IVA had a smaller effect than any of the treatments including ω-conotoxin GVIA ($P<0.001$). ω-Agatoxin IVA had a greater effect on DA efflux at 200 nM than at 15 nM ($P<0.01$), but still significantly smaller than any of the treatments that included ω-conotoxin GVIA ($P<0.01$).

In the medial axis of the CPu, all treatments also significantly reduced DA efflux for 1p (all $P<0.001$ vs.

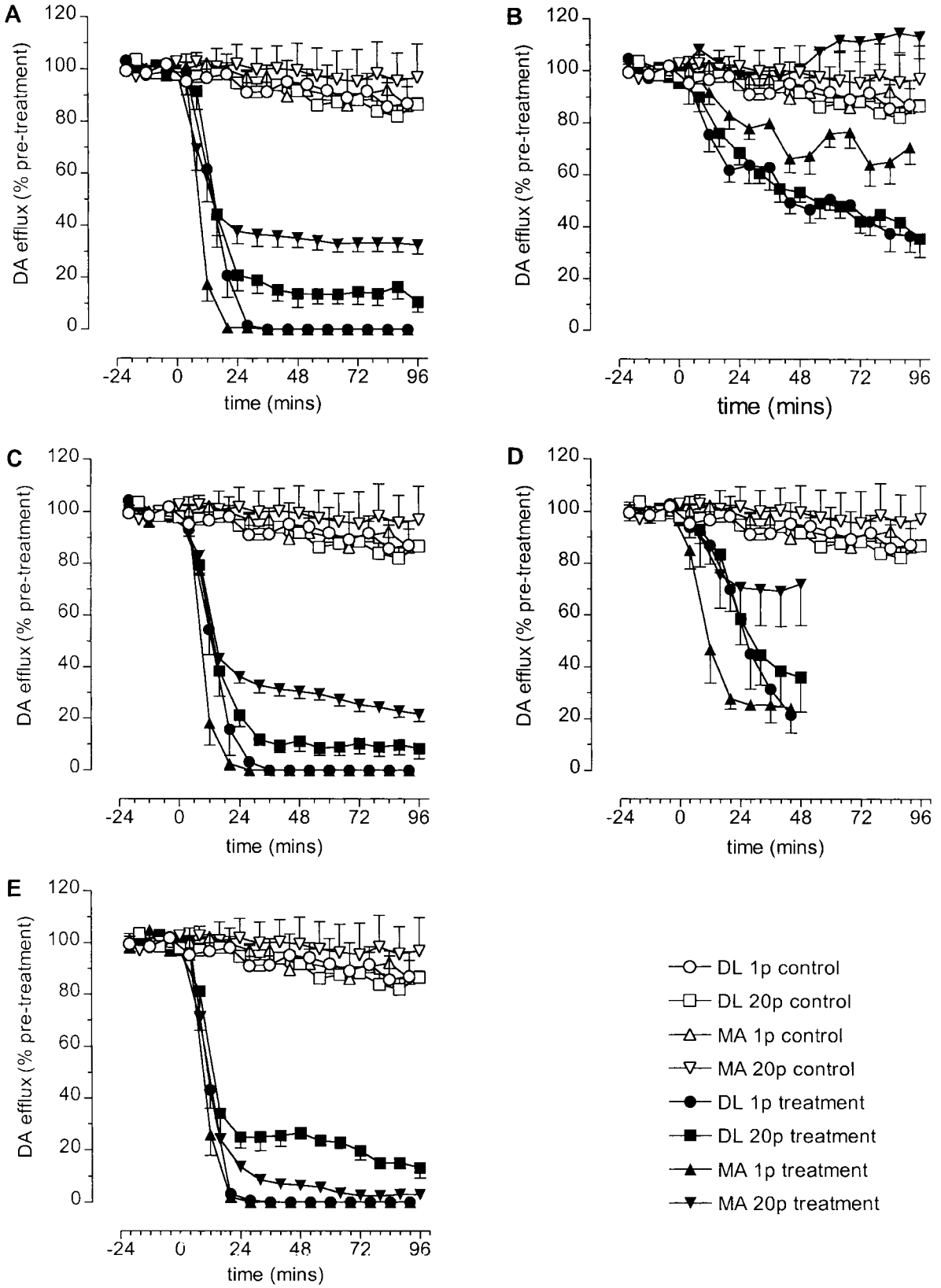

Fig. 2. The time-course of the effects of (A) 100 nM ω-conotoxin GVIA (n=5), (B) 15 nM ω-agatoxin IVA (n=4), (C) concurrent application (n=5) of 100 nM ω-conotoxin GVIA and 15 nM ω-agatoxin IVA, (D) 200 nM ω-agatoxin IVA (n=3) or (E) concurrent application (n=3) of 100 nM ω-conotoxin GVIA, 15 nM ω-agatoxin IVA and 500 nM ω-conotoxin MVIIC on DA efflux for 1p and 20p in dorsolateral and medial axis regions of the CPu. Toxins were added to the superfusant at time 0 and left in for 96 min or 48 min. Values are mean±S.E.M. Statistical analyses of these data are shown in figures below. DL, dorsolateral CPu; MA, medial axis of the CPu.

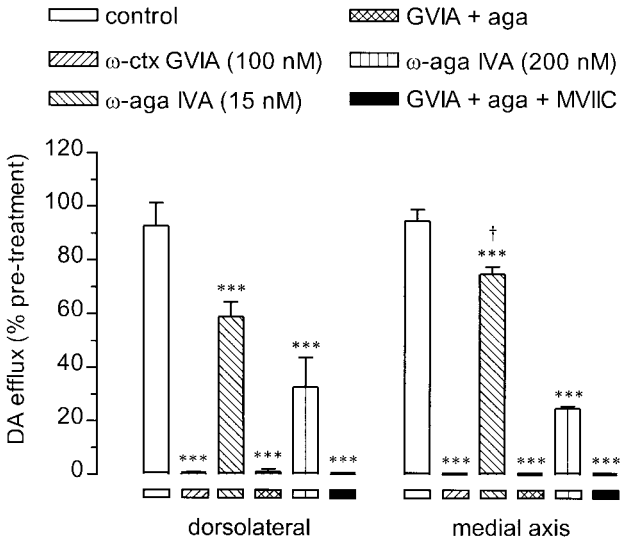

Fig. 3. The effect of voltage-operated calcium antagonists on DA efflux in dorsolateral and medial axis regions of the CPu for 1p electrical stimulations. Data shown are the average of three stimulations after 28–48 min exposure to the treatment (mean±S.E.M.). GVIA+aga refers to concurrent application of 100 nM ω-conotoxin GVIA and 15 nM ω-agatoxin IVA. GVIA+aga+MVIIC refers to concurrent application of 100 nM ω-conotoxin GVIA, 15 nM ω-agatoxin IVA and 500 nM ω-conotoxin MVIIC. ***$P<0.001$ vs. control (one-way ANOVA with post-hoc testing using Newman–Keuls Multiple Comparison Test). †$P<0.05$ vs. dorsolateral CPu (unpaired *t*-test).

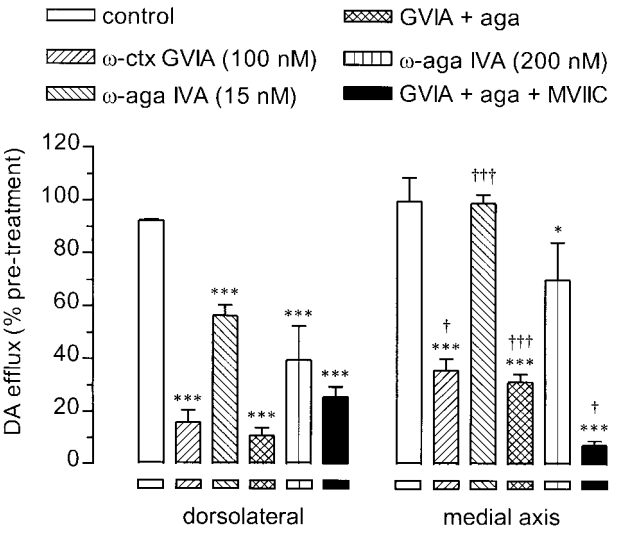

Fig. 4. The effect of voltage-operated calcium antagonists on DA efflux in dorsolateral and medial axis regions of the CPu for 20p electrical stimulations. Data shown are the average of three stimulations after 28–48 min exposure to the treatment (mean±S.E.M.). GVIA+aga refers to concurrent application of 100 nM ω-conotoxin GVIA and 15 nM ω-agatoxin IVA. GVIA+aga+MVIIC refers to concurrent application of 100 nM ω-conotoxin GVIA, 15 nM ω-agatoxin IVA and 500 nM ω-conotoxin MVIIC. *$P<0.05$; ***$P<0.001$ vs. control (one-way ANOVA with post-hoc testing using Newman–Keuls Multiple Comparison Test). †$P<0.05$; †††$P<0.001$ vs. dorsolateral CPu (unpaired *t*-test).

control; Fig. 3, right panel). ω-Conotoxin GVIA (alone or with other toxins) abolished DA efflux in all cases within 36 min. The effect of ω-agatoxin IVA was greater at 200 nM than at 15 nM ($P<0.001$), but at both doses it was smaller than any treatment including ω-conotoxin GVIA ($P<0.001$).

For 1p stimulations there was a regional difference in the effect of 15 nM ω-agatoxin IVA, which had a significantly greater effect in the dorsolateral region of the CPu ($P<0.05$).

3.2. Twenty-pulse stimulations ('burst' firing).

DA efflux for 20p in the dorsolateral CPu was significantly reduced by all the treatments (all $P<0.001$ vs. control; Fig. 4, left panel). None of the treatments including ω-conotoxin GVIA abolished DA efflux, but they did have a significantly greater effect than 15 nM ω-agatoxin IVA ($P<0.01$). The addition of other toxin(s) with ω-conotoxin GVIA had no further effect on DA efflux. ω-Agatoxin IVA applied at 200 nM had a significantly greater effect on DA efflux than at 15 nM ($P<0.05$), but still significantly smaller than 100 nM ω-conotoxin GVIA ($P<0.05$).

DA efflux for 20p in the medial axis of the CPu was reduced by ω-conotoxin GVIA treatments ($P<0.001$) and 200 nM ω-agatoxin IVA ($P<0.05$), but not 15 nM ω-agatoxin IVA (Fig. 4, right panel). Unlike for 1p stimulations, none of the treatments abolished DA efflux. Concurrent application of 15 nM ω-agatoxin IVA with ω-conotoxin GVIA had no further effect than for ω-conotoxin GVIA alone. However with 500 nM ω-conotoxin MVIIC also present, there was a further reduction in DA efflux ($P<0.05$). The effects of treatments including ω-conotoxin GVIA were greater than those for ω-agatoxin IVA at 15 nM ($P<0.001$) or 200 nM ($P<0.01$). ω-Agatoxin IVA had a greater effect at 200 nM than at 15 nM ($P<0.01$).

Smaller effects on DA efflux were observed in the medial axis than dorsolateral CPu with 100 nM ω-conotoxin GVIA ($P<0.05$), 15 nM ω-agatoxin IVA ($P<0.001$) or both ($P<0.001$). However the effect of concurrent application of 100 nM ω-conotoxin GVIA, 15 nM ω-agatoxin IVA and 500 nM ω-conotoxin MVIIC was greater in the medial axis ($P<0.05$). There was no regional difference in the effect of 200 nM ω-agatoxin IVA for 20p stimulations.

3.3. Comparison of stimulation paradigms in dorsolateral neostriatum

In the dorsolateral CPu, the effect of ω-agatoxin IVA (at either concentration) on DA efflux for 20p was not significantly different from that for 1p (Fig. 5, left panel). However, for all the treatments that included ω-conotoxin GVIA there was a significantly smaller effect on DA efflux for 20p than for 1p ($P<0.05$).

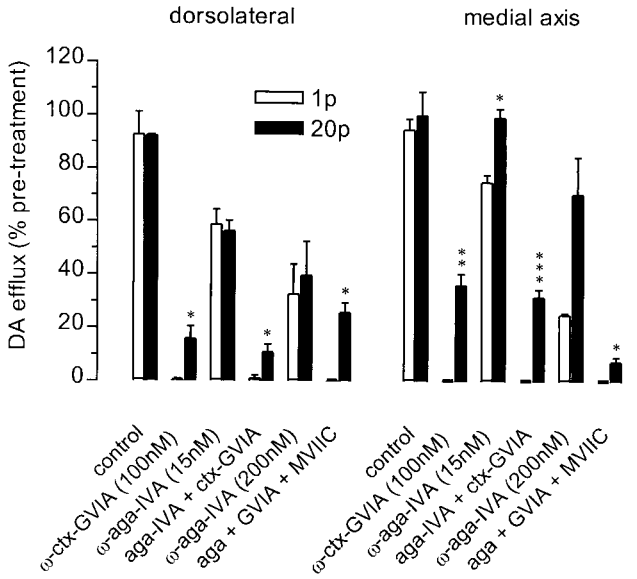

Fig. 5. The effect of voltage-operated calcium antagonists on DA efflux in dorsolateral and medial axis regions of the CPu for 1p and 20p electrical stimulations. Data shown are the average of three stimulations after 28–48 min exposure to the treatment (mean±S.E.M.). GVIA+aga refers to concurrent application of ω-conotoxin GVIA (100 nM) and ω-agatoxin IVA (15 nM). GVIA+aga+MVIIC refers to concurrent application of ω-conotoxin GVIA (100 nM), ω-agatoxin IVA (15 nM) and ω-conotoxin MVIIC (500 nM). *$P<0.05$; **$P<0.01$; ***$P<0.001$ vs. 1p stimulation (paired *t*-test).

3.4. Comparison of stimulation paradigms in the medial axis of the neostriatum

In the medial axis of the CPu, ω-agatoxin IVA did have a smaller effect on DA efflux for 20p than for 1p at 15 nM ($P<0.05$) but not at 200 nM (Fig. 5, right panel). All the treatments that included ω-conotoxin GVIA also had a smaller effect on 20p ($P<0.05$).

4. Discussion

Previous studies on dopamine and other transmitters suggest that low-voltage-activated VOCCs (T-type channels) are not involved in neurotransmitter release [30]. L-type channels are predominantly located in the cell bodies of neurones [13] and do not play a role in terminal calcium entry [26] or neurotransmitter release [6,18] where divorced from afferent action potential traffic, as here. The known pharmacology of the R-type channel is limited: it is insensitive to L-, N-, P- and Q-type channel blockers but can be blocked with low concentrations of inorganic nickel [15] that also block T-type channels. It is therefore difficult to attribute function to R-type channels without identifying them using electrophysiological channel recordings based on their biophysical characterisation [25].

As previously mentioned, midbrain DA cells typically fire in either a regular fashion or in short bursts separated by periods of silence [9]. These may be influenced by anaesthetics and neuroleptics amongst other drugs [19]. The pattern of terminal DA release induced by these different firing modalities is very different. In general, burst firing is a more efficient means of transducing action potentials into DA release [29]. Although many facets of the regulation of regular or burst firing and its ensuing DA release are known, the differential involvement of presynaptic VOCCs has not received attention. In the present study, we have therefore examined the regulation of DA release by various calcium channels in areas with different dopaminergic inputs. Single pulse stimulations were used to mimic regular neuronal firing, whereas 20p trains were used to model burst firing modalities.

Interpretation of blockade of VOCCs on DA release is not straightforward, since it does not directly affect DA release, but reduces the calcium entry required for release to take place. If intracellular calcium reaches a threshold level at the release apparatus associated with a docked synaptic vesicle following stimulation, the vesicle will be released. Blockade of a single channel subtype could reduce calcium entry below threshold at all docked vesicles and therefore abolish neurotransmitter release, even though the overall calcium current has not been reduced to zero i.e. other subtypes may still provide part of the current. Conversely, blockade of a channel that results in no effect on neurotransmitter release does not rule out its involvement, since calcium entry may have been reduced but not by enough that the intracellular calcium fails to reach threshold. Partial reduction of DA efflux by blockade of a VOCC subtype is probably due to reduction of the calcium entry below threshold at some (but not all) of the release sites.

Our data have demonstrated the involvement of N-, P- and Q-type VOCCs in striatal DA release, in agreement with other studies [4,7,8,12,14,18,32]. N-type channels had a greater effect on DA efflux than either P-, Q-type channels or both. The relative contribution of P- and Q-type channels could not be determined.

For 1p stimulations, DA efflux was abolished by concurrent blockade of N-, P- and Q-type channels (or by N-type channels alone). However, this was not true for 20p stimulations in either region of the CPu although DA efflux for 20p stimulations could be abolished by removal of calcium from the superfusant (data not shown). This suggests the involvement of another calcium channel (not N-, P- or Q-type) whose involvement in DA efflux was greater for ‘burst’ than ‘regular’ stimulation paradigms. This may be the R-type channel, a high-voltage activated VOCC that is resistant to the toxins used in this study, and has previously been implicated in neurotransmitter release [33]. This would be an attractive target for preferential calcium entry during burst firing since it deactivates faster

than the other channel subtypes, potentially allowing it to be reactivated by subsequent, rapidly arriving action potentials. However, with the limited knowledge of the pharmacology of the R-type channel at present, this could not be confirmed with the methodology used in this study.

The data also suggest that N-type channels and possibly P-type channels (in the medial axis at least) play a lesser role for 'burst' than 'regular' activation modalities. This is consistent with the findings of Turner et al. [32] who reported that blockade of N- and P-type channels was less effective in inhibiting striatal DA release for stronger depolarisations. Conversely, Q-type channels did not show a preferential role for 'regular' stimulations.

Regional differences in the involvement of VOCC subtypes in striatal DA release were also apparent. N- and P-type channels were both more important in the dorsolateral CPu than its medial axis, but Q-type channels played a greater role in the medial axis. The component of DA efflux insensitive to 15 nM ω-agatoxin IVA, 100 nM ω-conotoxin GVIA and 500 nM ω-conotoxin MVIIC for stimulation trains, was greater in dorsolateral CPu. This distribution of VOCCs subtypes may have important implications on the function of the striatal regions. It would appear that the dorsolateral CPu is better able to deal with 'regular' neuronal firing, since it has more N- and P-type but fewer Q-type channels, whereas the medial axis of the CPu may respond more efficiently to 'burst' firing. This is consistent with the observed function in these regions, where significantly greater DA efflux can be measured in the medial axis than the dorsolateral CPu for high frequency train stimulations [5]. Furthermore, burst firing is more common in A10 than A9 neurones [11].

In summary, this study demonstrates that N-, P- and Q-type VOCCs as well as at least one other route for entry of extracellular calcium are involved in DA release in the CPu. N-type channels were more influential than P/Q-type channels. N-type channels played a greater role in DA release in the dorsolateral CPu than its medial axis, as did P-type channels. N-type channels were more important for 1p 'regular' stimulations than for 20p 'burst' stimulations although there was no difference in the overall P/Q-type channel involvement between stimulation paradigms in either region. The differential involvement of VOCC subtypes for different firing patterns may be a mechanism by which neurones are able to integrate patterned cell activity.

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