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A comparison of the effects of the dopamine partial agonists aripiprazole and (−)-3-PPP with quinpirole on stimulated dopamine release in the rat striatum: Studies using fast cyclic voltammetry in vitro

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ABSTRACT

The effects of aripiprazole, (−)-(3-hydroxyphenyl)-N-n-propylpiperidine ((−)-3-PPP) and quinpirole on single and multiple pulse stimulated dopamine release were investigated using the technique of fast cyclic voltammetry (FCV) in isolated rat striatal slices. Aripiprazole and (−)-3-PPP had no significant effect on single pulse dopamine release at concentrations from 10 nM to 10 μM indicating low agonist activity. The compounds failed to potentiate 5 pulse stimulated release of dopamine although inhibitory effects were seen at 10 μM for aripiprazole. Both compounds were tested against the concentration–response curve for quinpirole's inhibition of stimulated single pulse dopamine release. Aripiprazole and (−)-3-PPP shifted the concentration–response curve for quinpirole to the right. In each case this was greater than a 100-fold shift for the 10 μM test compound. Whilst these results indicate that both compounds show little agonist activity on dopamine release and significant antagonism of the inhibitory effect of quinpirole on dopamine release, whether they are functionally selective dopamine D_2 ligands remains controversial.

1. Introduction

Fast cyclic voltammetry (FCV) is a technique that can measure in real time the release of dopamine from rat striatal slices. It is therefore a useful tool to accurately assess the efficacy of dopamine D_2 agonists and partial agonists on stimulated single and multiple pulse dopamine release (Bull and Sheehan, 1991; Palij et al., 1990; Trout and Kruk, 1992). Full agonism may be tested on single pulse stimulated release, as the endogenously released dopamine will have no effect on the dopamine D_2 presynaptic autoreceptors. Full antagonism can be measured by either using a suitable multiple pulse protocol where endogenous dopamine D_2 autoreceptors are activated, or assessing the ability of the compound in question to inhibit the effect of a full agonist such as quinpirole on dopamine release (Limberger et al., 1991).

Aripiprazole is an atypical antipsychotic and antidepressant used in the treatment of schizophrenia, bipolar disorder, and clinical depression. Aripiprazole's mechanism of action is different from those of other FDA-approved atypical antipsychotics (e.g., clozapine, olanzapine, quetiapine, ziprasidone, and risperidone). Rather than antagonizing the dopamine D_2 receptor, aripiprazole acts as a dopamine D_2 and 5-HT_{1A} receptor partial agonist (K_i = 0.34 nM and 1.65 nM respectively, Lawler et al., 1999). It can significantly increase dopamine levels in the prefrontal cortex of rats but only at low concentrations (Zocchi et al., 2005).

(−)-3-PPP has also been shown to have some antipsychotic action but not sustained receptor desensitization. It has been used in schizophrenia possibly by attenuating dopamine function in two different ways, by stimulating the presynaptic receptors and blocking the postsynaptic receptors. It has previously been reported that in contrast to racemic 3-PPP, (+)-3-PPP can inhibit electrically evoked release of both [^{3}H]dopamine and [^{14}C]acetylcholine from superfused rat neostriatal slices (Mulder et al., 1985). In contrast (−)-3-PPP did not have inhibitory effects on dopamine release but antagonized those effects of (+)-3-PPP. Both enantiomers can reduce increases in striatal dopamine synthesis produced by γ-butyrolactone, although the (−) enantiomer was only partially active (Clark et al., 1984). 3-PPP has also been shown not to protect against MPTP-induced dopaminergic neurotoxicity (Muralikrishnan et al., 2004). In contrast to the above compounds quinpirole has previously been shown by us and other groups to act as a full agonist inhibiting dopamine release in the rat striatum with high potency (for example see (Palij et al., 1990; O'Neill et al., 2009)).

The determination of the functional intrinsic activity of partial agonist compounds at dopamine D_2 receptors is a difficult task when carried out in brain native tissues. The aim of the study was to

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quantify the potential partial agonist and antagonist activity of (−)-3-PPP and the dopamine D_2 partial agonist, aripiprazole, on pre-synaptic dopamine D_2 auto-receptors located in the terminals of dopamine neurons in the rat striatum using FCV. We have also compared the effect of these compounds with that of the full agonist quinpirole.

2. Materials and methods

2.1. Electrochemical system

2.1.1. Generation of the signal

Fast cyclic voltammetry (FCV) is an electrochemical technique designed to enable detection of monoamine release in real time (see Stamford, 1990 for a comprehensive review). Its advantages are the speed of recording and the small size of the working electrode (typically 7 μm diameter by 50 μm length). A three electrode configuration is typically used in brain slice FCV, namely an auxiliary electrode, working electrode and reference electrode. The reference electrode is a silver/silver chloride electrode (A-M Systems, Inc, WA) whilst the auxiliary electrode is also a Ag/AgCl electrode but bridged from the bath in a plastic pipette tip filled with 1 M NaCl. Fast cyclic voltammetry (FCV) was carried out using a Millar Voltammeter (Dr. Julian Millar, Queen Mary & Westfield College, University of London, UK) connected to an FCV headstage (see Millar and Barnett, 1988 for a full circuit diagram of the apparatus). The FCV amplifier subjects the working electrode to a triphasic set of anodic and cathodic voltage sweeps in a period of 20 ms. The triphasic voltage waveform ramps from 0 to −1.0 V to +1.4 V to −1.0 V to 0 (20 ms) equating to a scan of 480 V/s. Throughout our experiments this waveform was applied to the potentiostat four times a second. Because the scan only lasts 20 ms, it can be repeated many times a second if required. The input triphasic ramp pattern for FCV in these experiments is shown in Fig. 1A. The FCV headstage circuit measures the working electrode current (generated by the drive voltage) and from this current the concentration of electrically oxidizable or 'electroactive' material at the tip of the working electrode can be computed.

2.1.2. Faradaic current

Following the triphasic voltage input into the working electrode a background current is monitored that is due to the complex impedance characteristics of the electrode/electrolyte interface (Fig. 1B). When electroactive materials such as dopamine are present on the surface of the electrode extra current flow is generated through the electrode. This electron influx is known as the faradaic current (Fig. 1C) and includes both oxidation and reduction peaks, for dopamine, characteristically +600 mV and −200 mV respectively. To provide information on dopamine release dynamics, a sample and hold circuit was set to monitor current at +600 mV on each successive scan. The typical output from this display is shown in Fig. 1D in response to dopamine.

2.1.3. Carbon fiber electrode manufacture

Carbon fiber electrodes were home manufactured but see also Armstrong-James and Millar (1979). A borosilicate capillary tube (1 mm i.d.) was filled with acetone and a single carbon fiber inserted (7 μm diameter). Upon drying the tube the capillary was pulled by an electrode-puller (P97, Sutter Instrument, Novato, USA) giving

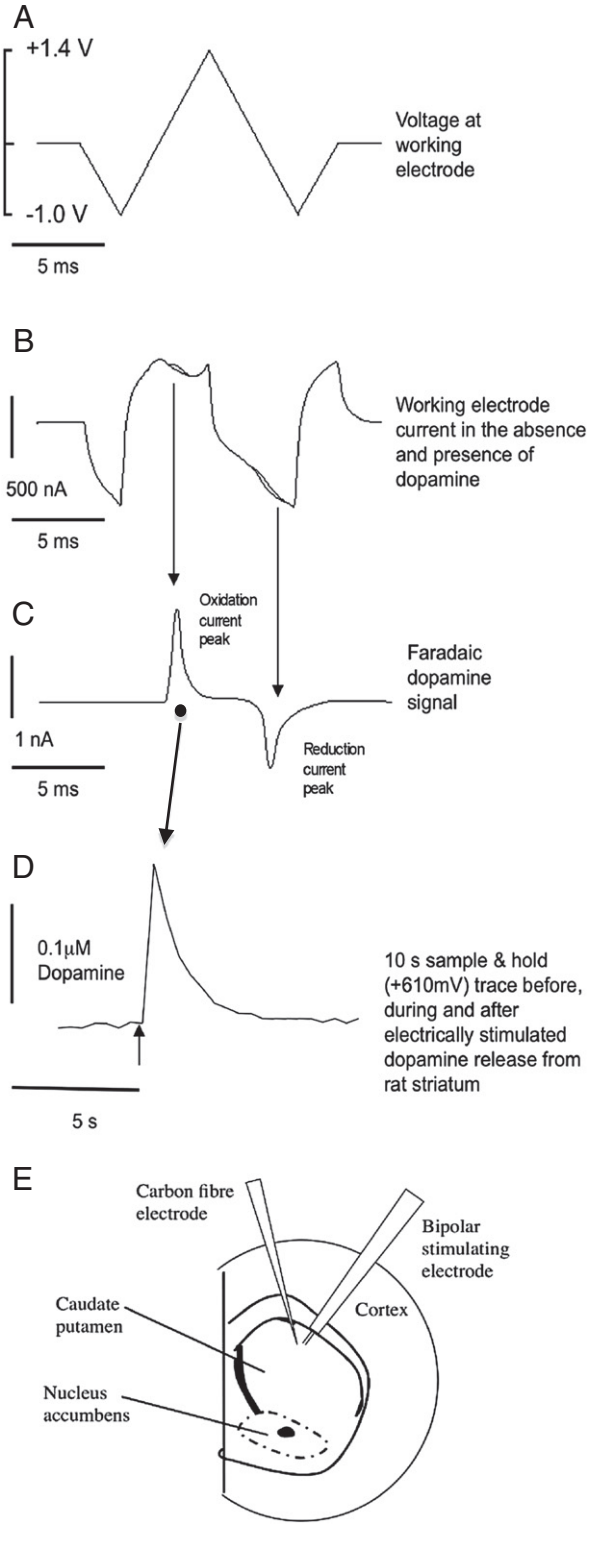

Fig. 1. Waveforms used in fast cyclic voltammetry (FCV). A. A triphasic voltage ramp is passed down the carbon fiber electrode four times per second (4 Hz). The ramp sweeps from 0 V (relative to silver/silver chloride reference electrode) to −1.0 V to +1.4 V to −1.0 V and back to 0 V. This sweep lasts 20 ms. B. The resultant current measured by the carbon fiber electrode is called the charging current. Superimposed on the charging current is the current obtained when the electrode is placed in a ringer solution containing 1 μM dopamine. C. If the charging current in B in the absence of dopamine is subtracted from that current in the presence of dopamine a trace typical of C is the result (subtractogram). This is known as the faradaic current and is the result of the oxidation and reduction of dopamine on the surface of the carbon fiber electrode. Dopamine oxidizes at approximately +610 mV and is reduced at approximately −200 mV. D. The trace illustrated in D is the result of a sample and hold device measuring at +610 mV during the electrical stimulation of the striatum. The arrow indicates the time of stimulation of striatum (0.1 ms pulse width; 10 V). Post calibration of the CFMe indicated that approximately 0.1 μM dopamine is evoked by a single electrical stimulation in the dorsolateral striatum. Peak rise time is approximately 0.5 s and half decay time approximately 1.0 s. E. Placement of electrodes. Schematic diagram illustrating the placement of the carbon fiber microelectrode (recording electrode) and the bipolar stimulating electrodes (tip separation 200 μm) in the dorsolateral striatum. The carbon fiber electrode was placed 100 to 200 μm from the bipolar stimulating electrodes most commonly in the region illustrated.