Dasotraline – Evaluation of its dopamine reuptake characteristics in comparison to stimulants and non-stimulants by microdialysis in the nucleus accumbens of freely-moving rats

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**INTRODUCTION**

Dasotraline is a novel DAT, NET and SERT reuptake inhibitor that is being developed as a new treatment for ADHD. Dasotraline has high affinity for cloned human reuptake transporters for dopamine (DAT), norepinephrine (norepinephrine; NET) and 5-hydroxytryptamine (serotonin; SERT) in vitro (Kd = 26, 27 and 39 nM, respectively). Dasotraline shows similar potency to inhibit monoamine uptake into cell-lines transfected with these transporters (IC50 [nM]: DAT = 3.0, NET = 4.1 and SERT = 14.9).

In vivo microdialysis is a powerful tool for characterising the actions of drugs on monoamine neurotransmitters and their metabolites. In addition, it can provide information about the pharmacological mechanism of action of drugs in this study. We have used microdialysis to investigate dasotraline’s effects on the extracellular concentrations of dopamine and its major metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA). Dasotraline has been profiled in parallel with other drugs that are either approved to treat ADHD or have been reported to have efficacy in this indication. They were the stimulant reuptake inhibitor, methylphenidate, the monoamine releasing agents, d-amphetamine and phentermine, and the weak selective dopamine reuptake inhibitor, bupropion.

**METHODS**

Microdialysis probes (CMA 12 Elite, 2 mm tip) were implanted into the nucleus accumbens (AP +2.2 mm, ML ±1.5 mm relative to bregma, DV -8.0 mm relative to skull surface) of isoflurane anaesthetised male, Sprague Dawley rats (300±50g).

After 24 h recovery, 20 min samples (1.2 μL/min artificial CSF) were taken from freely-moving rats for 4 h following drug administration. Doses (mg/kg): dasotraline (1, 3 and 10), methylphenidate (1, 3 and 10), d-amphetamine (0.1, 0.3, 1 and 3), phentermine (1, 3 and 9), bupropion (10, 30 and 50), vehicle (50 mM acetate buffer: 5 mL/kg). Drugs were administered by intraperitoneal (ip) injection. Figures are truncated at 3 h for clarity.

Dopamine, DOPAC and HVA were measured by Alexys™ HPLC-ECD (Antec Scientific).

**RESULTS**

Basal extracellular concentrations, 80 min pre-drug, were (vehicle treated controls): dopamine = 5.4 ± 0.05 fmol/5μl, DOPAC = 1895 ± 29 fmol/5μl and HVA = 1196 ± 6 fmol/5μl.

Dasotraline produced dose-dependent, gradual and sustained increases in dopamine efflux maximal at 160 min (Figure 1A) with concomitant falls in DOPAC, but not HVA (Figures 2A, 3A).

Methylphenidate produced a dose-dependent, rapid increase in dopamine efflux that was maximal at 40 min and declined rapidly thereafter (Figure 1B). There was no dose-effect ceiling. Methylphenidate reduced extracellular DOPAC, but not HVA (Figures 2B, 3B).

d-Amphetamine and phentermine produced dose-dependent, rapid increases in dopamine efflux that were maximal at 40 min and declined rapidly thereafter (Figures 1C, 1D). There was no dose-effect ceiling. d-Amphetamine and phentermine decreased DOPAC and HVA (Figures 2C, 2D, 3C, 3D).

Bupropion increased extracellular dopamine with maximum effects at 20-40 min (Figure 1E). There was a clear dose-effect ceiling for bupropion. Bupropion produced concomitant falls in DOPAC, but not HVA (Figures 2E, 3E).

**CONCLUSIONS**

- Dasotraline evoked gradual, dose-dependent and sustained increases in dopamine efflux in the nucleus accumbens.
- In contrast, the stimulants exemplified by the releasing agents, d-amphetamine and phentermine, and reuptake inhibitor, methylphenidate, produced rapid, large increases in dopamine efflux with no dose-effect ceiling and of relatively short duration.
- Dasotraline’s pharmacology is clearly different from that of the dopaminergic stimulants and also the weak dopamine reuptake inhibitor, bupropion.

The results indicate that pharmacologically relevant doses of dasotraline (1.3 mg/kg) produce relatively small increases in the synaptic concentration of dopamine.