A comparison using in vivo microdialysis of the catecholaminergic profiles of dexamphetamine and dl-threo-methylphenidate in an animal model of ADHD.

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INTRODUCTION
Dexamphetamine (d-AMP) and dl-threo-methylphenidate (dl-MPH) are effective and well established treatments for attention deficit hyperactivity disorder (ADHD). Although both drugs are believed to produce their therapeutic actions by increasing dopamine (DA) and noradrenaline (NA) neurotransmission in the brain, their catecholaminergic profiles have not been previously compared in an animal model of attention deficit hyperactivity disorder (ADHD).

To achieve this objective, we performed dual-probe microdialysis experiments in young, spontaneously hypertensive (SH) rats because they are hyperactive, impulsive and inattentive and these are the core symptoms of ADHD.

MATERIALS AND METHODS
Male SH rats (250–320g; Charles River, UK) were anaesthetised using isoflurane (5% to induce, 2% to maintain) in an O₂/N₂O mixture (1 litre/min each). Two concentric dialysis probes (CMA, UK, 2 mm tip for cortex, 4mm tip for striatum) were stereotaxically implanted into the prefrontal cortex (PFC) (coordinates: AP: +3.2 mm; L: -2.5 mm relative to bregma; V: -4.0 mm relative to the skull surface) and striatum (STR) (AP: +0.2 mm; L: +3.0 mm; V: -7.8 mm). Coordinates are according to Paxinos and Watson.

Rats underwent a recovery period of at least 16 h, during which time food and water were available ad libitum and probes were continuously perfused with an artificial cerebrospinal fluid (Harvard Apparatus, UK) at a flow rate of 1.2 µl/min. Four basal samples (15 min interval) were collected prior to intraperitoneal (ip) administration of drugs (d-AMP 1 or 3 mg/kg and dl-MPH 10 mg/kg or 20 mg/kg) or saline. Sample collection continued for 3 h (d-AMP) or 4 h (dl-MPH) post-drug administration into Eppendorf vials which contained 5.0 µl of 0.1 M perchloric acid to prevent oxidation. Samples were stored at -80°C until analysis for DA* and NA* by HPLC with electrochemical detection. Values are mean ± SEM (n = 8-13) and statistical comparisons were made between drug- and saline-treated groups by one-way ANCOVA with Williams’ test for multiple comparisons.

KEY FINDINGS
- Figures 1-4 unequivocally demonstrate that d-AMP and dl-MPH produce very large increases in extraneuronal concentrations of NA in the PFC and DA in the STR of the SH rat.
- Although d-AMP (3 mg/kg) and dl-MPH (20 mg/kg) evoked peak increases in NA in the PFC of similar magnitudes, ie 649±87% versus 469±87% (Figures 1 and 2), d-AMP had a much more powerful effect to potentiate striatal DA efflux, ie 459±1912% versus 729±232% (Figures 3 and 4).
- Both drugs have a very rapid onset of peak effect on NA or DA overflow, ie ~45 min.

REFERENCES

CONCLUSIONS
- From these experiments performed in SH rats, it is evident that d-AMP and dl-MPH both markedly enhance NA and DA efflux in the PFC and STR in this rat model of ADHD.
- d-AMP has a more powerful effect on the efflux of DA (STR) than on NA (PFC), whereas dl-MPH has a more balanced spectrum of action.
- Using doses that reflect their differential in the clinical setting, the magnitude of the effect of d-AMP on DA and NA efflux was 6.7x (STR) and 1.4x (PFC) greater than those of dl-MPH.
- These findings almost certainly reflect the fact that although d-AMP and dl-MPH are both reuptake inhibitors, in the case of d-AMP, this action is combined with the more powerful mechanism of firing-independent, catecholamine release, and possibly also, inhibition of MAO.

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