Characterisation of the catecholaminergic profiles of methylphenidate and its enantiomers in an animal model of ADHD by in vivo microdialysis.

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INTRODUCTION
Attention deficit hyperactivity disorder (ADHD) is characterised by four primary symptoms, i.e. impulsiveness, inattentiveness, distractibility and overactivity. These abnormalities are also present in the behavioural repertoire of the spontaneously hypertensive rat (SHR), and consequently, this strain has been proposed to be an excellent model of human ADHD1-3, 6

dl-Methylphenidate (dl-MPH), which is an established treatment for attention deficit hyperactivity disorder (ADHD), exists as 2 enantiomers, i.e. d- and l-MPH. This study has determined the contribution of their effects to the actions of the parent racemate (dl-MPH) on extracellular levels of dopamine (DA) in the striatum and noradrenaline (NA) in the frontal cortex of freely-moving SHRs using dual-probe microdialysis.

MATERIALS AND METHODS
Male, SHRs (250–290 g; Charles River, UK) were anaesthetised using isoflurane (5% to induce, 2% to maintain) in an O2/N2O mixture (1 litre/min each). A concentric dialysis probe (CMA, UK, 2 mm tip) was stereotaxically implanted into the prefrontal cortex (coordinates: AP: +3.2 mm; L: +/-2.5 mm relative to bregma; V: –4.0 mm relative to the skull surface) and striatum (AP: +0.2 mm; L: +/-3.0 mm; V: –7.8 mm). Coordinates are according to Paxinos and Watson4.

Rats underwent a recovery period of at least 16 h during which 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 drug or saline. Sample collection continued for 4 h 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 DA5 and NA6 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.

RESULTS
Figures 1 and 2 show that the parent racemate, dl-MPH, produced rapid dose-related elevations in the efflux of striatal DA and cortical NA with maximum increases ~60min after dosing. The effects on extraneuronal concentrations of DA were approximately twice as great as on NA, ie at 20mg/kg 729 ± 232% (p<0.001) versus 469 ± 69% (p<0.001) compared to baseline. However the effects on NA were longer lasting being significantly higher than baseline at the end of the experiment, whereas DA had returned to control values at this time.

Figures 3 and 4 show the pharmacodynamics of the effects of dl-MPH were similar to those of the racemate with peak increases in DA and NA of 1042 ± 117% (p<0.001) and 449 ± 51% (p<0.001), respectively. By contrast, the l-enantiomer was much less potent producing only a 200 ± 24% (p<0.01) increase in DA efflux with no significant effect on NA.

REFERENCES

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