Differences in presynaptic mechanisms of the ADHD drugs, d-amphetamine and methylphenidate, revealed by "neurochemical fingerprinting": correlations between dopamine neurochemistry and behavioural function

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INTRODUCTION

The psychostimulants, d-amphetamine (AMP) and methylphenidate (MPH), are currently the most widely used drugs for the treatment of attention deficit hyperactivity disorder (ADHD). Microdialysis experiments in freely-moving rats have shown that both drugs produce rapid, profound increases (>500%) in striatal dopamine (DA) efflux with no dose-effect ceiling (Heal et al, 2009a). Dopamine mimetic drugs with different presynaptic mechanisms each produce a unique pattern of changes in dopamine metabolites ("neurochemical fingerprints") in the brains of C57/BL6 mice (Heal et al, 2009b). We have extended these findings by comparing the behavioural and neurochemical actions of the catecholamine releasing agent, AMP, and the stimulant reuptake inhibitor, MPH. In this series of experiments, we have determined the effects of both drugs on striatal concentrations of DA and its metabolites ("neurochemical fingerprints"), locomotor activity and stereotypy, and possible correlations between these parameters.

METHODS

Individual, adult, male C57/BL6 mice (n = 6-17) were acclimatised to cages in an automated photobeam activity system and then intraperitoneally (ip) injected with AMP (1, 3 or 10 mg/kg), MPH (10, 20 or 30 mg/kg) or saline (10 mL/kg). (Cheetham et al, 1996). 3-MT was determined by HPLC-ECD according to Heal et al (1990).

SUMMARY

- The dopaminergic effects of AMP are consistent with firing-independent release, reduced DA reuptake together with in vivo inhibition of MAO.
- MPH increased HVA accumulation revealing that striatal DA turnover was increased. In contrast, conventional DA reuptake inhibitors, eg GBR12909, reduced DOPAC accumulation, but do not alter HVA (Heal et al, 2009b) indicating that DA turnover is reduced.
- The action of MPH on DA efflux is firing-dependent (Nomikos et al, 1990; Butcher et al, 1991). Together, these findings indicate that MPH does not function as a conventional DA reuptake inhibitor and firing-dependent DA release is an important component of its mechanism of action.
- Neurochemical fingerprinting also revealed that stereotypy responses to AMP and MPH correlated with striatal concentrations of different dopamine metabolites, ie 3-MT and HVA, respectively.
- These results provide further evidence to demonstrate the versatility and predictive validity of neurochemical fingerprinting as a screening technique.

REFERENCES

- Cheetham et al, 1996, Neuropharm, 35: 63-70
- Heal et al, 2009a, Neuropharm, 57: 608-18
- Heal et al, 2009b. SfN abstract 421.2/D16

Fig 1. Locomotor activity

Fig 2. Neurochemical fingerprints of d-amphetamine and methylphenidate

Fig 3. Correlations between stereotypy scores and the striatal concentrations of various dopamine metabolites