Profiles of lisdexamfetamine, methylphenidate and modafinil in rats trained to discriminate d-amfetamine from saline

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INTRODUCTION
Lisdexamfetamine (LDX; Vyvanse®) is a prodrug for the management of ADHD that is metabolised in red blood cells to yield d-amfetamine (d-AMF) and L-lysine (Pennick 2010). Methylphenidate and modafinil are also stimulants. Methylphenidate is a Controlled Drug in the UK, but modafinil is not. All three compounds have been shown to be effective medications to treat ADHD.

Data from studies in drug-experienced human volunteers (Jasinski & Krishnan, 2009a,b) suggest that the unusual pharmacokinetics of LDX may reduce some of its liability for abuse.

The aim of this study was to explore the subjective experience of LDX in rats which had been trained to distinguish d-AMF from saline in a two-choice, operant drug-discrimination procedure. We compared it with methylphenidate, d-AMF and modafinil. LDX, d-AMF and methylphenidate were tested after dosing by the oral (po) and intraperitoneal (ip) routes to evaluate the effects on their potency of switching to a non-clinical route of administration. Modafinil was only investigated after ip administration.

METHODS
Groups of 6-9 adult female PVG rats were trained to discriminate d-AMF (0.5 mg/kg) from saline in a 2-lever operant procedure (partial generalisation = 26-74%; full generalisation ≥75% responding on the appropriate lever) using an FR-5 schedule of food rewards. Drug-discrimination is a well established model for determining similarities between the subjective effects of test compounds in comparison to reference drugs with known abuse liability profiles. LDX was tested at various times (15, 60 and 120 min) after administration, methylphenidate and d-AMF were tested at 15 min and modafinil at 30 and 60 min after ip dosing.

To facilitate comparisons between LDX and d-AMF, doses of both drugs are expressed in terms of mg/kg d-AMF base. Doses of methylphenidate and modafinil are expressed as mg/kg base.

RESULTS
• When tested 15 min after dosing, orally administered d-AMF (0.1-1.5 mg/kg) dose-dependently generalised to the d-AMF cue (Fig. 1). At this time-point, methylphenidate (3.0-10 mg/kg, po) also dose-dependently generalised to d-AMF (Fig. 1).
• Fifteen (15) min after po dosing, LDX (equivalent to 0.5-1.5 mg/kg d-AMF base) generalised to saline. At 60 min, LDX partially generalised to d-AMF at 0.5-1.0 mg/kg and fully generalised at 1.5 mg/kg. At 120 min, LDX (0.5 and 0.75 mg/kg) generalised to saline and LDX (1.0 and 1.5 mg/kg) partially generalised to d-AMF (Fig. 2; Table 1).
• Modafinil (100-200mg/kg ip) partially generalised to d-AMF 60 min after dosing (Fig. 3). 5/9 rats receiving modafinil (150 mg/kg) generalised fully to the d-AMF cue. Decreasing the interval to 30 min did not increase the effect of modafinil (50-150 mg/kg ip) with 3/5 rats generalising to d-AMF at 150 mg/kg.
• Switching to the ip route reduced the time interval required for LDX (0.5-1.5 mg/kg) to be recognised as d-AMF-like, but it did not alter its potency (Fig. 4, top).
• Intraperitoneal administration of d-AMF (0.1-0.5 mg/kg) dose-dependently generalised to the d-AMF cue. However, the dose required for full generalisation decreased from 1.5 mg/kg po to 0.5 mg/kg ip (Fig. 4, middle).
• After ip administration, methylphenidate (0.75-3.0mg/kg) dose-dependently generalised to d-AMF and the dose required for full generalisation decreased from 10 mg/kg po to 3.0 mg/kg ip (Fig. 4, bottom).

CONCLUSIONS
• Generalisation to d-AMF occurred rapidly after po or ip administration of methylphenidate.
• Although LDX generalised to the d-AMF cue, its d-AMF-like subjective effects were delayed in onset after oral dosing and of relatively short duration.
• The subjective effects of modafinil were recognised as somewhat d-AMF-like. LDX and modafinil were similar by virtue of their delayed onset of effect and predominantly partial generalisation to d-AMF.
• The potencies of methylphenidate and d-AMF were increased ~3 fold when dosing was switched from oral administration to the ip route.
• In contrast, the potency of LDX was not increased by switching to the ip route.
• Consistent with Jasinski and Krishnan’s human findings (2009a,b), these data support the hypothesis that unlike methylphenidate or d-AMF, the recreational abuse potential of LDX cannot be enhanced by switching to the more harmful route.

REFERENCES

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