A microdialysis and behavioural comparison of lisdexamfetamine, methylphenidate and modafinil in freely-moving rats

Helen Rowley1, Rajiv Kulkarni1, David Hackett2, David Heal1
RenaSci Ltd, Nottingham, UK1; Shire Pharmaceuticals Ltd, Basingstoke, UK2

RESULTS

• The intermediate [therapeutic] doses of LDX, methylphenidate and modafinil increased efflux of NA and DA in the PFC (Fig 1A,B,C). The effects of LDX on DA and NA were slower in onset than those of methylphenidate or modafinil, but more consistently significant at later time-points. LDX significantly increased the efflux of NA, DA and 5-HT across all doses, whereas the profile of methylphenidate and modafinil changed with dose. Methylphenidate had no enhancing effect on 5-HT, while modafinil increased 5-HT only at the highest [supra-therapeutic] dose (Fig 1D).

• The intermediate dose of LDX elevated the efflux of DA and sporadically also 5-HT in STR, whereas methylphenidate and modafinil produced only very small elevations of DA with no effect on 5-HT (Fig 2A,B,C). Although methylphenidate and modafinil enhanced striatal DA efflux, their effects were smaller than LDX and at two doses methylphenidate actually decreased 5-HT. Only the highest dose of methylphenidate enhanced 5-HT (Fig 2D).

• The intermediate doses of LDX and methylphenidate caused transient significant increases locomotor activity at one or two time-points, while the intermediate (but not the lowest) dose of modafinil produced a small, but prolonged, increase of activity. Sustained and significant elevations in locomotor activity were only seen after administration of the highest [supra-therapeutic] doses of LDX, methylphenidate and modafinil (data not shown).

• At the highest doses of LDX and methylphenidate, significant correlations existed between extracellular DA concentration and the magnitude of locomotor activity (Fig. 3). The slope of the relationship was much steeper for methylphenidate than for LDX. No such correlation was found with modafinil.

CONCLUSIONS

• The pharmacological profile of LDX was markedly different from methylphenidate and modafinil by virtue of its action to increase the extracellular levels of DA, NA and 5-HT in PFC and DA and 5-HT in STR. By contrast, the therapeutically equivalent doses of methylphenidate and modafinil had an exclusively catecholaminergic action.

• The profile of LDX on central monoaminergic function was very consistent across doses, whereas those of methylphenidate and modafinil were not. At pharmacologically relevant doses, LDX produced larger and more sustained increases in the extracellular concentrations of monoamines in the PFC and STR than methylphenidate or modafinil.

• LDX produced much larger increases in striatal DA efflux than methylphenidate or modafinil with a less propensity to induce locomotor activation.

• 5-HT has an attenuating influence on dopaminergic neurotransmission in the STR and this may account for the less stimulant profile compared with methylphenidate.

• Together, these preclinical data predict that LDX may provide a greater separation between efficacy and stimulant adverse events in the clinical situation than immediate-release methylphenidate or modafinil.

REFERENCES


ACKNOWLEDGMENTS

Funding Statement: This research carried out by RenaSci Ltd was funded by the sponsor, Shire Pharmaceuticals Development Ltd.