PROJECT REVIEW

"*Cardiovascular and central actions of drugs classed as stimulants*"

Dr. Docherty, (Royal College of Surgeons, Ireland)

Stimulants are banned in competition by the World Anti-Doping Agency, except for a small number of therapeutic agents subject to monitoring, and a large number of compounds have been placed on the prohibited list. However, a number of agents available as over the counter medicines for therapeutic uses, although subject to monitoring, may enhance performance. In addition, a large number of other unlisted stimulants are available, some of which appear in athlete's samples. There is only very limited information on the relative potencies of even monitored agents as stimulants. For some agents even the mode of action is not well understood. This project seeks to supply that information. In this project, the stimulant actions of a wide range of compounds, prohibited, specified, monitored or unlisted, will be investigated in pharmacological and physiological bioassays in an animal model. This study will provide data giving direct measurement of the relative potencies of a wide range of stimulants at a number of biomarkers of stimulant action. The results will allow informed decisions on the doping potential of monitored substances relative to prohibited or unlisted substances. The wider implications are that these bioassays can be quickly performed to give robust information on any new compound appearing in athlete samples or to decide on the acceptable agents and doses for approved therapeutic uses. Generation and dissemination of detailed pharmacological information is essential to prevent doping in sport and to provide alternative therapies.

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Results and Conclusion

1. Bupropion is a stronger noradrenaline reuptake blocker than previously reported. It is likely to have both peripheral cardiovascular stimulant actions and central behavioural actions in doses used clinically.
2. The majority of direct adrenoceptor stimulants investigated in this study showed relatively high potency as β-adrenoceptor agonists in producing a tachycardia. Although β1-adrenoceptor stimulation may be of limited benefit in sport (see Davis et al., 2008), this merits further consideration, especially if some of these agents are found to have additional β2-adrenoceptor agonist actions.
3. Cathine is likely to be an α2-adrenoceptor agonist, and this merits further study, as central clonidine-like actions as well as peripheral actions may be important for this agent.
4. Selective actions at α1D-adrenoceptors occur for a number of agents. It is unclear if this action is of benefit in enhancing performance. This merits further investigation.
5. Locomotor studies by telemetry are a useful method to study central stimulant actions. Both bupropion and modafinil were found to have central stimulant actions in doses employed.
6. A large amount of data have been obtained on the cardiovascular effects of 12 receptor stimulants, and on the peripheral and central effects of 3 monoamine transporter blockers. On publication, this will greatly increase the literature on the pharmacology of these agents. On acceptance for publication, copies of these papers will be forwarded to WADA.

Presentations/Publications

Killian, L. & Docherty, J.R. Cardiovascular stimulant actions of bupropion acting at the noradrenaline transporter Presentation to the British Pharmacological Society, London Meeting Dec 2012.

Killian, L.M. & Docherty, J.R. (2014). Cardiovascular stimulant actions of bupropion in comparison to cocaine in the rat. Eur. J. Pharmacol. (full paper, awaiting final acceptance).

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Thesis

Killian, L.M. Cardiovascular actions of drugs classed as stimulants. M.Sc. thesis submitted Feb 2014, RCSI, Dublin.