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Cardiovascular stimulant actions of bupropion acting at the noradrenaline transporter

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Introduction: Stimulants are banned in competition by the World Anti-Doping Agency, except for a small number of therapeutic agents subject to monitoring (see Docherty, 2008). However, a number of agents available as over the counter medicines for therapeutic uses, although subject to monitoring, may enhance performance. Among these is bupropion. Bupropion is reported to be a weak antidepressant, acting as a weak blocker of the monoamine re-uptake transporters, is widely available for the treatment of tobacco dependence (see Docherty, 2008), and has been reported to enhance exercise performance (Watson et al., 2005). We have examined in detail the potency of bupropion in comparison with cocaine as a blocker of the noradrenaline re-uptake transporter in peripheral tissues of the rat.

Methods: Male Wistar rats (250-350g) were killed by anaesthesia with pentobarbitone (60 mg/kg, i.p.) and cervical dislocation for in vitro studies, or anaesthetized with pentobarbitone (60 mg/kg, i.p.) for blood pressure recording. Epididymal portions of rat vas deferens were stimulated every 5 min with a single stimulus and rat right ventricular strips were paced at a frequency of 1 Hz (0.5 ms pulses, supramaximal voltage) using a Grass S88 stimulator. Test drugs were assessed against nerve evoked contractions in vas deferens, and in terms of their ability to potentiate contractions to noradrenaline in rat ventricle. In anaesthetized rats, noradrenaline (0.3 mg/kg) was given i.v. at 5 min intervals until consistent pressor responses had been obtained, and effects of test drug were assessed against these pressor responses.

Results: In 1 Hz paced right ventricular strips, cocaine (10 μM) significantly increased the potency of noradrenaline at increasing the force of contraction. Similarly, bupropion (30 μM) significantly increased the potency of noradrenaline in ventricular strips. To obtain more accurate relative potencies, further studies were carried out with a range of concentrations in rat vas deferens. In rat vas deferens, bupropion and cocaine produced significant concentration-dependent increases in the contractile response to nerve stimulation (analysis of variance and Dunnett test, $P<0.05$), with potency (pEC50) values of 5.14±0.29 (n=6) for bupropion and 6.01±0.30 (n=6) for cocaine. Hence, cocaine was approximately 7.5 times more potent than bupropion in rat vas deferens. In the anaesthetised rat, cocaine and bupropion significantly increased the pressor response to noradrenaline at doses of 0.3 and 1mg/kg, respectively (analysis of variance and Dunnett test, $P<0.05$). Bupropion (3mg/kg) increased the noradrenaline pressor response to 149.0±14.4% of control (n=7; $P<0.05$). Overall, cocaine was approximately 3-10 times more potent than bupropion in vivo in the rat. Since bupropion is used clinically in doses of up to 300 mg (approximately 4mg/kg), it is likely that bupropion has actions at the noradrenaline transporter in these doses.

Conclusion: Bupropion may have peripheral cardiovascular stimulant actions by blockade of the noradrenaline transporter in doses used clinically in man. This may explain findings of increased exercise performance with bupropion.

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