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Comparison of actions of stimulants acting at the noradrenaline transporter with those of desipramine

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We have compared the actions of the stimulants bupropion, adranifil and modafinil with those of the noradrenaline transporter (NET) blockers cocaine and desipramine. 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). We have investigated the actions of bupropion, a substance subject to monitoring, and two agents banned in competition: adranifil and modafinil. Bupropion is 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). Adrafinil and modafinil increase alertness and are thought to act at least partly by activation of central noradrenergic systems. We have examined in detail the potency of these substances in comparison with cocaine and desipramine as NET blockers in the rat.

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 (0.5 ms pulses, supramaximal voltage) using a Grass S88 stimulator. Test drugs were assessed against nerve evoked contractions in vas deferens. In anaesthetized rats, noradrenaline (1 μg/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.

In rat vas deferens, cocaine and bupropion produced significant concentration-dependent increases in the contractile response to nerve stimulation (analysis of variance and Dunnett test, $P<0.05$). Hence, cocaine was 5-10 times more potent than bupropion in rat vas deferens. Adrafinil, modafinil, and, perhaps surprisingly, desipramine failed to produce a significant potentiation of the contractile response to nerve stimulation in rat vas deferens. However, in the anaesthetised rat, cocaine (0.3mg/kg), desipramine (0.3mg/kg) and bupropion (1mg/kg) significantly increased the pressor response to noradrenaline to 142±7%, 129±6% & 129±7% of control respectively (analysis of variance and Dunnett test, $P<0.05$). Overall, cocaine and desipramine were equipotent, and were approximately 3-10 times more potent than bupropion in vivo in the rat. Adrafinil and modafinil (3 mg/kg) failed to affect pressor responses to noradrenaline. Desipramine was equipotent with cocaine against pressor responses in vivo, but was ineffective in the vas deferens in vitro, due presumably to α_1-adrenoceptor antagonism.

Bupropion, but not adrafinil or modafinil, has peripheral cardiovascular stimulant actions by blockade of the NET in doses used clinically in man. Desipramine had

similar actions as cocaine against pressor responses in the anaesthetized rat but not against contractile responses in rat vas deferens. Desipramine may additionally block α_1-adrenoceptors in rat vas deferens over the same range of concentrations it produces uptake blockade.

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