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COMMENTARY

Cannabis reward: biased towards the fairer sex?

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In contrast to drugs such as alcohol, amphetamine and cocaine, cannabis use in humans has proven difficult to model in laboratory animals. Recent breakthrough discoveries of intravenous THC self-administration in rhesus monkeys and self-administration of the synthetic cannabinoid agonist WIN 55,212-2 in rats have allowed new studies of the genetic, neural and environmental determinants of cannabis use. In the present issue of BJP, Fattore and colleagues further demonstrate genetic (strain) differences in WIN 55,212-2 self-administration in rats, with Long Evans (LE) and Lister Hooded (LH), but not Sprague–Dawley, rats self-administering this drug. They then show that female LE and LH rats self-administer more WIN 55,212-2 than male rats. Ovariectomy abolished this sex difference, suggesting a permissive role for oestrogen in cannabis reward. This accompanying Commentary reviews recent progress in animal models of cannabis use and highlights the role of genetic, developmental and endocrine factors in driving cannabis use and dependence.
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Abbreviations: LE, Long Evans; LH, Lister hooded; NIDA, National Institute on Drug Abuse; THC, delta-9-tetrahydrocannabinol; WIN 55,212-2, (*R*(+)-[2,3-dihydro-5-methyl-3-[(morpholinyl)methyl]- pyrrolo[1,2,3-de]-1,4 benzoxazinyl]-(1-naphthalenyl)-methanone mesylate]

Cannabis is the most widely used illicit drug in the world and is generally considered to have only modest addictive potential compared to other drugs such as nicotine, heroin or methamphetamine. However, some users do become dependent on cannabis, consuming the drug in a compulsive fashion and experiencing dysphoria during abstinence. The factors determining vulnerability to cannabis dependence have proven difficult to untangle in human studies. In this issue of the *British Journal of Pharmacology,* Fattore *et al*. (2007), provide evidence from an animal model of hitherto unexpected sex differences in cannabinoid intake in rats.

Self-administration studies provide a superior animal model of human drug use with high face validity. The avid self-administration of alcohol, nicotine, cocaine and methamphetamine by rodents has been of great utility to addiction scientists. However, cannabis self-administration has proven notoriously difficult to obtain in laboratory animals. A breakthrough came in 2000, when Stephen Goldberg and colleagues at NIDA showed self-administration of the prototypical natural cannabinoid THC in squirrel monkeys (Tanda *et al*., 2000). The critical factor appeared to be the use of very low intravenous doses of THC, analogous to the doses present in a puff of cannabis smoke. Soon after this, Fattore *et al*. (2001) showed intravenous self-administration of low doses of the synthetic cannabinoid CB1 receptor agonist, WIN 55212-2 in rats, albeit with the limitation that rats must be chronically food restricted for this to occur.

Genes play a critical role in determining the proclivity towards cannabis consumption. Earlier studies involving intracranial self-stimulation and place preference models indicated that different genetic strains of rats had different motivational responses to cannabinoids, with Lewis and Long Evans (LE) but not Fischer 344 strain rats seen as 'cannabis preferring' (Lepore *et al*., 1995; Gardner, 2002). Corresponding strain differences in cannabinoid-induced brain activation and mesolimbic dopamine release were also evident (Arnold *et al*., 2001). More recently, WIN 55212-2 self-administration was reported in Lister Hooded (LH) and LE rats, but not in Sprague–Dawley rats, who will not self-administer the drug (Deiana *et al*., 2007).

Cannabis has intake-limiting panic and anxiety-inducing properties in a subset of human users and has anxiogenic and aversive properties in rats (McGregor *et al*., 1996; Quinn *et al*., 2007). If such an aversive component could be minimized then the rewarding actions of cannabinoids might be unmasked. Accordingly, the apparently 'reward-resistant' Sprague–Dawley strain, will self-administer THC directly into the nucleus accumbens and ventral tegmental area, presumably bypassing the aversive effects of cannabinoid stimulation of other brain sites that occur with systemic administration (Zangen *et al*., 2006).

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A genetic predisposition towards or away from cannabis is also hinted at in human studies. A fascinating early study involving identical twins in New Zealand indicated that the extent to which cannabis is perceived as pleasurable or aversive appears at least partly genetically determined (Lyons *et al*., 1997). A more recent study showed that single-nucleotide polymorphisms in the cannabinoid receptor 1 gene can be associated with vulnerability towards cannabis dependence in cannabis-using adolescents (Hopfer *et al*., 2006).

What of the gender factor? In general, intravenous self-administration studies show female rats outstripping males in their acquisition of a drug taking habit and their overall drug intake, particularly with stimulants (Lynch, 2006). Fattore *et al*. (2007), now show that female LH and LE rats maintain a higher level of response for WIN 55212-2 than their male counterparts. On first glance these results deduced from rats seem to largely conflict with human population studies reporting higher rates of cannabis intake in males than females. However, societal factors contribute to such statistics (for example higher social disapproval of female drug use) which do not necessarily imply that females find cannabis less rewarding than males (Reed and Mowbray, 1999). Indeed, recent survey results indicate that adolescent females in the USA are now overtaking males in their rates of initiation of cannabis use (ONDCP, 2006). Other human research suggests that women progress through the various stages of drug addiction at an accelerated rate, entering treatment programmes earlier than men (Brady and Randall, 1999; Westermeyer and Boedicker, 2000).

The heightened cannabinoid self-administration seen in female rats is diminished by ovariectomy (Fattore *et al*., 2007). This oestrogenic modulation of the reinforcing effects of cannabinoids, mirrors that seen with stimulant drugs (Lynch, 2006). Oestrogen has powerful anxiolytic effects in rats that involves endocannabinoids (Hill *et al*., 2007). Thus oestrogen may minimize the aversive effects of cannabinoids, unmasking a euphorogenic effect. In addition, CB1 receptors and oestrogen receptors interact in the mesolimbic dopamine system (Freund *et al*., 2003; Weiser *et al*., 2007), with administration of THC increasing dopamine activity in this system in an oestrogen-sensitive fashion (Bonnin *et al*., 1993). Recent findings indicate that adolescent rats find cannabinoids less aversive than adult rats, and it is conceivable that a hormonal influence is also at play here (Quinn *et al*., 2007).

Humans of course are not 'large rats' and the behavioural influence of oestrogen is generally far more pronounced in female rats than in female humans. Indeed, one important study found that cannabis intake in women does not vary across menstrual cycle phases (Griffin *et al*., 1986). Another caveat is that higher rates of self-administration in rats can sometimes reflect lower rewarding efficacy (that is more drug is self-administered to compensate for diminished rewarding effects): it would be reassuring to see these sex differences in rats extended using other complementary animal models of drug reward.

Finally, recent research indicates that repeated cannabinoid exposure can have lasting adverse residual effects on social behaviour, emotionality and cognitive function in rats (Quinn *et al*., 2007) and such effects may be more pronounced in adolescent female rats (O'Shea *et al*., 2004). Human studies also highlight adolescent female populations as particularly prone to anxiety and depressive disorders when cannabis is used heavily (Patton *et al*., 2002). Oxytocin, a neuropeptide strongly linked to oestrogen, is downregulated in mesolimbic sites by chronic cannabinoid exposure (Butovsky *et al*., 2006), and this may play a critical role in cannabis-withdrawal symptoms (Cui *et al*., 2001). Exploration of an oestrogen and oxytocin-linked component in the negative lasting impacts of chronic cannabis use would therefore appear a worthwhile avenue for future research.

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Conflict of interest

The authors state no conflict of interest.

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