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Cannabis antagonists: a new era of social psychopharmacology?

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The recent announcements by Synthelabo-Sanofi that their cannabis (CB1) receptor antagonist Rimonabant has shown efficacy in treating obesity and improving lipid profiles, as well as in assisting in smoking cessation (Anthenelli and Despres, 2004), suggests that we are about to enter a new era of psychopharmacology. For the first time, we will have an antagonist to the most highly expressed G-protein coupled receptor in human brain – there are more CB1 receptors in brain than the total of all dopamine, serotonin and noradrenaline receptors combined. Despite the discovery of endogenous cannabinoids over a decade ago, the role of these receptors has not been clear, although the advent of antagonists and the development of CB1 knockout mice have begun to clarify this question.

The most obvious role of CB1 receptors is to mediate the effects of cannabis (or more correctly Δ9-THC, the active metabolite). Evidence for this comes from observations that CB1 receptor antagonists block the effects of cannabis and that they can also precipitate withdrawal when given to humans stabilized on cannabis. This raises the possibility that such antagonists could be used to treat cannabis dependence by preventing access of drug to the receptor, thus preventing use and possibly extinguishing desire in the same way that the opiate antagonist naltrexone is used in opiate dependence. Although cannabis dependence is relatively uncommon in users, the extensive use of cannabis (up to 50% of individuals aged under 30 years in some samples) means that there are a significant number of individuals reporting such dependence on cannabis. Estimates vary depending by country (Nutt and Nash, 2002) and, in the UK, approximately 10% of individuals presenting to drug treatment services in the UK report some degree of cannabis dependence (Home Office Report on Cannabis, 2002).

There are other perhaps more widely applicable, but more controversial, uses of antagonists to minimize the social harms from cannabis. One area is in schizophrenia where cannabis is well known to exacerbate psychotic experiences and precipitate psychotic episodes *de novo* in vulnerable individuals (Verdoux and Tournier, 2004; Arseneault *et al*., 2004). In such cases, it is possible that cannabis antagonists might act as therapeutic reversal agents in a similar way to the benzodiazepine antagonist flumazenil, reversing the effects of benzodiazepine intoxication.

A more contentious possibility is the use of cannabis antagonists to offset any residual effects of cannabis used socially. Many individuals in important jobs use cannabis in their leisure time and carryover from this may lead to dangerous performance (e.g. when they work in the transport industry). An antagonist would prevent carryover impairment, provided that it had a longer duration of action compared to that of cannabis, and could have real value in improving public safety.

Another related aspect is in response to work place drug testing. The long half-life of cannabis metabolites means that individuals can test positive days after use when they are completely free from any effects of intoxication. This can result in them being banned from work because it is impossible to know for certain that they do not have some degree of neurocognitive impairment. An antagonist of reasonable duration (e.g. 8 h) could theoretically be used as a 'failsafe' to ensure that they were not impaired throughout the working day and would be able to work safely. In many ways, this approach resembles the common use of caffeine to offset the impairments produced by excess alcohol taken the night before. It could allow a large group of cannabis-using individuals to be accepted back into the workplace again.

If cannabis antagonists are free of unwanted actions, it is likely that they might become widely available – perhaps even over-the-counter for weight loss or smoking cessation. Individuals would then be in a position to use antagonists to modify the effects of cannabis use in a socially responsible manner. Such a scenario would require acceptance of the value of the harm reduction as opposed to the prohibition/deterrent approach to illicit drug use. To an extent, the use of self-medication in preventing drug problems has already become accepted for nicotine and heroin. Nicotine gum is available without prescription for smokers who wish to stop. In some opiate treatment services, the antagonist naloxone is given to heroin addicts for use as a reversal agent in the case of accidental overdose in their friends (Dettmer *et al*., 2001). Cannabis antagonists have a potential utility in the wider public arena, and may perhaps begin a new era in social psychopharmacology?

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