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Chemical names

AM374: palmityl-sulfonyl-fluoride

AM404: *N*-(4-hydroxy-phenyl)-arachidonylamine

JWH133: 3-(1′,1′-dimethylbutyl)-1-deoxy-Δ^8-tetrahydrocannabinol

SR141716A: *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazone-3-carboxamide

SR144528: *N*-([1s]-endo-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)-pyrazolone-3-carboxamide

WIN552122: (*R*)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl) pyrrolo [1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphathalenylmethanone

Reply: a sanguine approach to cannabis

The comments of Di Marzo *et al.* provide a balanced synopsis of our findings[1] and raise some important questions for which answers are emerging. One comment that pertains to our initial study was the dose level used and the possible psychotropic side-effects of intravenous cannabinoids. We did not carry out a rigorous dose–response study of the compounds used and, although some doses could be considered to be in the 'high' range, these compounds could produce anti-spastic effects with no evidence of a loss of body temperature. This latter aspect forms part of the tetrad test (body temperature, ring catalepsy, activity in the open field and analgesia) to elucidate psychoactive neurobehavioral activity of cannabinoids in rodents. Owing to the presence of CB_1 receptors in motor and cognitive centres, it is possible that CB_1 receptor agonism might lead to psychotropic effects, which is one of the challenges that must be overcome in the clinical use of cannabis. Although apparently evident in mice, it remains to be seen to what extent an acceptable 'threshold' for symptomatic benefit over adverse psychoactivity can be achieved in patients, if direct CB_1 receptor agonism is the target.

Our data suggest that the beneficial effects of cannabinoids on spasticity and tremor were transient (lasting for hours) but could be observed following repeated administration (D. Baker *et al.*, unpublished). This indicates the likelihood that regular administration of cannabinoids is required to sustain effects in humans, which probably makes the direct intravenous route impractical therapeutically. However, this route was examined for experimental purposes in the first instance because routes of administration made an impact on the therapeutic outcome. This was particularly evident with Δ^9-tetrahydrocannabinol (THC), which had minimal effect when injected intraperitoneally[1]. This raises the question of appropriate routes for clinical application, a problem again highlighted recently in a clinical anecdote[2]. Although smoking is not an acceptable option, cannabinoids are highly lipophilic and are slowly released following ingestion. They are susceptible to 'first pass' effects when administered via the venous portal system as could be encountered via the oral and intraperitoneal routes. There might therefore be therapeutic advantage from a more direct intravenous route, such as spraying or inhaling directly into the vascular beds in the mouth or lungs to provide a 'hit' to the receptor system. We now have an experimental system to address these issues. Is this the beginning, or the beginning of the end, of cannabis as a medication? Can we move from the plant into the arena of pharmaceutical-based medicines for the treatment of human diseases? The future holds the answers.

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0165-6147/00/$ – see front matter PII: S0165-6147(00)01486-3