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INTRINSIC ACTIVITY

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MEETING ABSTRACT

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Cannabinoids: complexity at every level on the path to therapeutic exploitation – plant cannabinoids, endocannabinoids, target receptors, transforming enzymes

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The *Cannabis* plant is amongst the oldest cultivated plants; exploited for its fibre and for the unique metabolites it contains. Despite the centuries of contact, understanding of the nature of the unique metabolites (which may number up to 100) present in the plant is very much more recent. The two best studied are Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is a tricyclic component responsible for the psychoactivity associated with consuming preparations from the *Cannabis* plant, while CBD is a related bicyclic structure with promise as an anti-epileptic. The synthetic pathway in the *Cannabis* plant involves carboxylated versions of these agents, with evidence for extensive variation in content dependent on genetics, geography, cultivation method, anatomical region, harvesting and storage.

The molecular targets of THC in human are two G protein-coupled receptors, CB_1 and CB_2, which are activated by two families of fatty-acid derivatives, the most well-understood of which are anandamide (*N*-arachidonoylethanolamine) and 2-arachidonoylglycerol. Although these are both eicosanoid derivatives, they are synthesised and hydrolysed by independent routes, and have been reported to act at numerous molecular targets beyond CB_1 and CB_2 cannabinoid receptors. Both anandamide and 2-arachidonoylglycerol have been identified to be hydrolysed by multiple hydrolases, as well as being subject to oxidation by cyclooxygenase, lipoxygenase and cytochrome P450 routes. Furthermore, the endocannabinoids are capable of activating ligand-gated ion channels, such as the TRPV1 vanilloid receptor, and nuclear hormone receptors, such as the peroxisome proliferator-activated receptors. The enzymes which hydrolyse and transform these endocannabinoids also have a range of endogenous metabolites which act as substrates. These further substrates (and products) are biologically active in their own right, many with profiles extending beyond the receptors, channels and enzymes mentioned above.

The challenge for the next phase of cannabinoid research is to acknowledge and exploit this complexity to generate therapeutically useful agents from the many selective pharmacological tools currently available. An additional obstacle for cannabinoid research is the growing number of countries and states permitting medicinal and/or recreational *Cannabis*. Dealing with issues like quality control and delivery of the preparations of *Cannabis* to minimise harm and maximise 'benefit' will not be trivial.

Keywords: *Cannabis* – cannabinoids – G protein-coupled receptors – hydrolytic enzymes – ion channels

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