299P PSYCHOACTIVE CANNABINOIDS AND MEMBRANE SIGNALLING: A PUTATIVE MECHANISM

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Psychoactive, THC-like cannabinoids partition into the lipid bilayer of the membrane, altering membrane fluidity and activating phospholipases. As a result, increased production of lipid signalling molecules, arachidonyl ethanolamide (AEA), arachidonyl diglycerol (2AG) and arachidonic acid with its cascade of eicosanoids, especially prostaglandins, are generated. Cyclooxygenase inhibitors (indomethacin) block THC-induced prostaglandin biosynthesis. THC and psychoactive cannabinoids also bind persistently to G protein membrane receptors. This binding is associated with allosteric changes in neurotransmitter receptor response, which is increased (dopamine, catechols, GABA), or decreased (acetylcholine, NMDA, opiate (μ and β)). These responses are often biphasic. Identified endogenous transmitters to the THC (G protein) receptor are membrane lipids (AEA and 2AG).

It is proposed that AEA and 2AG receptor interaction possesses a physiological function that is to regulate the signalling between boundary lipid and the receptors or enzymes of the membrane. The boundary lipids surrounding the membrane proteins are the vehicles for putative signals between the AEA-G protein receptor and the neurotransmitter receptors. The change of configuration of the G protein receptor catalysed by the lipid mediators would modulate the signalling effect of the membrane on its constituent enzymes and receptors. AEA and 2AG, by-products of tbe membrane phospholipids, would thus be indirect signal modulators of membrane activity. Stimulation of the AEA-G protein receptors might maintain the membrane lipid bilayer in a homeodynamic equilibrium, associated with the transmission of instantaneous signalling to enzymes and neurotransmitter receptors in the lipid bilayer. These signalling mechanisms between membrane phospholigands, the G receptor protein and the lipid bilayer are an ubiquitous property of all membranes and have been identified in brain synapses, gametes, and gonads. The fundamental nature of the AEA and 2AG lipid mediators in controlling membrane function is supported by, in the case of AEA, at least two biosynthetic mechanisms, namely direct enzyme-mediated esterification of phosphatidylethanolamine by free arachidonic acid and, secondly, by a transesterification reaction from phosphatidylcholine. The endogenous natural ligands, AEA and 2AG, which have the same binding sites on the G protein receptor as THC, are signalling molecules generated from the membrane phospholipids and have misleadingly been identified with "cannabinoids".

It is hypothesized that interaction of these lipid mediators with G proteins might initiate signalling through a physical change in protein conformation. Furthermore, the physical signal to the boundary layer lipid would be transduced to the membrane enzyme which initiates the phospholipid-AEA (or 2AG) cycle, thus completing a closed physicochemical loop. Regulation of this process would depend on the interaction of the lipid mediators with their receptors which, in turn, would modulate the signalling function of the lipid bilayer in response to physiological stimuli. In order to perform its putative physiological signalling function, the physicochemical properties of the bilayer must retain their physiological integrity. However, THC alters the physicochemical composition and structure of the membrane and, instead of being rapidly recycled like AEA, must be entirely excreted from the body and will thus remain in the body for a considerable time. THC deregulates the putative membrane signalling in two ways: firstly, by activating the AEA and LAG receptors and, secondly, by altering the physicochemical organization of the boundary lipid bilayer into which it partitions. THC thus deregulates the physiological signalling role of the lipid bilayer, a fundamental feature of all living cells. AEA and 2AG should be regarded as members of a class of fundamental membrane signalling molecules which modulate the activity of G protein receptors, rather than "endogenous cannabinoids".

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300P THE AGE FACTOR IN THERAPEUTICS

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The ageing of populations in both the developed and developing world has highlighted the growth of the pharmaceuticals market for older patients, targeted at disorders of high prevalence and a minority of more or less age-related disorders. In many settings, the escalation of prescribing for older people represents the bulk of market increase in recent years.

Concern over iatrogenic problems has, over the last three decades, motivated investigation of prescribing rationale, medication management and the effect of age on the adaptive mechanisms involved in drug disposition and pharmacodynamics. Those issues have been largely clarified and incorporated into the culture of drug regulation, though there is still a need for further research and for continued interpretation and application within clinical practice.

Together with this, the use of drugs as probes in preclinical and clinical gerontology has enhanced the understanding of age-related processes, particularly at the interface between healthy ageing and disease.

By rectifying the historical exclusion of older patients from preliminary and large scale clinical drug trials, it has been made clear that a positive clinical outcome with modern drug therapy is characteristic of appropriate patient groups of advanced chronological age. There can therefore no longer be any justification for failing to address this dimension of clinical evaluation within drug development programmes and the introduction of clinical guidelines.

There is now a pressing need and opportunity to consolidate this field of enquiry to receive radically the approach taken to therapeutics in late life and to investigate systematically the role of ageing processes in the disorders of older age and their treatment. Such a strategic initiative in age research (as distinct from consideration of ageing as a corollary) will provide a more logical and better informed rationale for the identification, development and application of new drug molecules and therapeutic interventions for the future