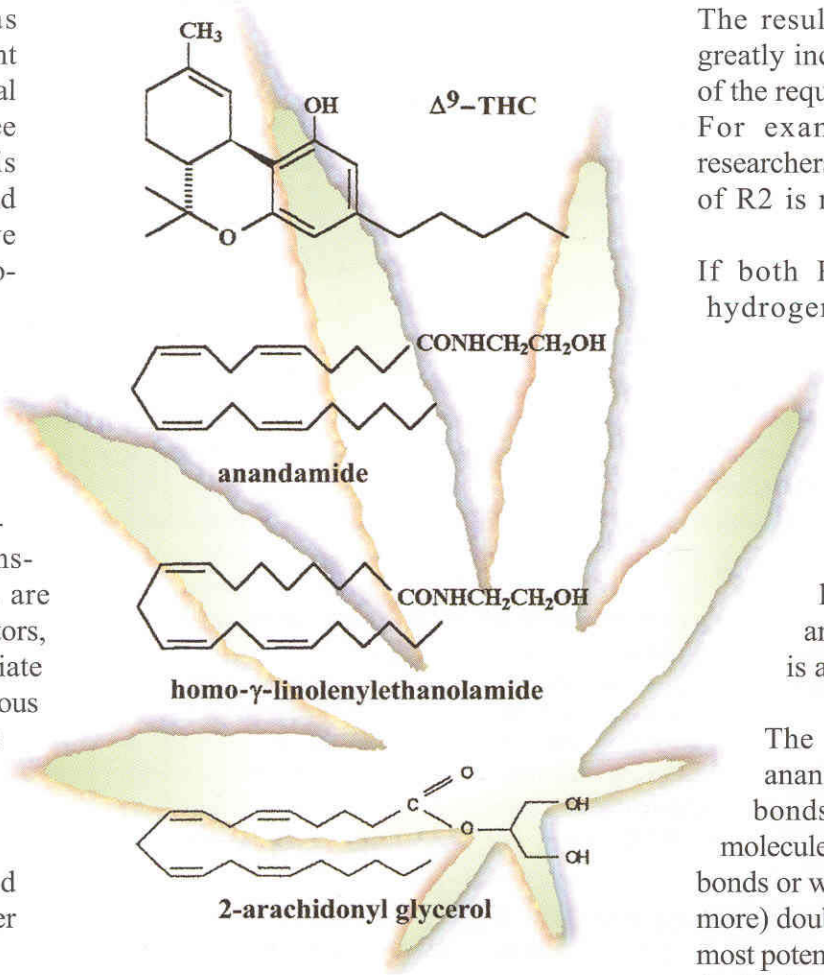
RESEARCH NOTES: Cannabis "Look-Alike" Molecules

Cannabis (marijuana) has been used by many societies, ancient and modern, as a natural pharmaceutical and mood-altering agent. ISF grantee Prof. Raphael Mechoulam and his colleagues were the first to isolate and determine the structure of the active ingredient of cannabis, Δ^9 tetrahydro-cannabinol (THC).

More recently, investigators have found that mammals, including humans, have two distinct populations of THC receptors, both of which are GTP-binding, protein-coupled molecules with seven trans-membrane regions. CB1 receptors are found largely in the brain; CB2 receptors, in immune cells. Since the body's opiate receptors are designed to bind endogenous opiate molecules, namely enkephalins and endorphins, not plant extracts (opium, heroin), it is reasonable to expect that the body's THC receptors are similarly designed to bind endogenous molecules (ligands), rather than THC.



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In 1992 Prof. Mechoulam's group found the first such endogenous agent, anandamide, a brain chemical which binds CB1 and produces many of the same biological and behavioral effects as THC. Soon thereafter they isolated two more biologically active CB1 ligands from the brain and one from the gut (see chemical structures above), leading to questions about which chemical features most affect their biological function -- that is, about their structure-activity relationship (SAR).

Prof. Mechoulam, Prof. Zvi Vogel and their colleagues have synthesized over 50 anandamide-like molecules and tested their ability to bind the CB1 receptor *in vitro*. In particular, in anandamide, the nitrogen atom (N) is attached to two chemical groups, H (R1) and CH2-CH2-OH (R2), both of which can readily be replaced (substituted). The results of these studies have greatly increased our understanding of the requirements for CB1 binding. For example, surprisingly, the researchers found that the -OH group of R2 is not required for binding.

If both R1 and R2 are merely hydrogen (H), the molecule is inactive. If one of them is merely hydrogen and one is an akyl group, the molecule is active (the investigators checked this up to a branched pentyl group). If, however, both hydrogens are replaced by an akyl group, the molecule is again inactive.

The core molecule can (as in anandamide) have four double bonds, or even just three; but molecules with only 0, 1 or 2 double bonds or with 5 or 6 (and presumably more) double bonds are inactive. The most potent compound tested had four double bonds, R1=H and R2=CH2-CH2-CH3. It had a KI of about 11.7 nM. Anandamide came in fifth, with a KI of 38.2 nM. However, the *in vitro* SAR for these compounds, based on CB1-binding, does not necessarily correlate with their *in vivo* SAR based on biological effects, and the latter are now being investigated.

The researchers also found that, although THC, anandamide and 11-hydroxyl-cannibinol bind to both CB1 and CB2 receptors with roughly equal strength, they inhibit the adenylyl-cyclase enzyme strongly via binding to CB1, but only weakly via CB2. Such differences in signal pathway activation could, perhaps, be exploited to design new therapeutic agents which affect gut receptor (CB2) but not brain receptor (CB1) signals. Such drugs might, for example, have THC's anti-inflammatory properties without its psychoactive effects.