

whereas the third bound to the β -barrel formed at the interface of the two monomer subunits.

Analogue synthesis allowed optimization of each of these series (to give **2** and **3**). Furthermore, as they bound at distinct sites on the E2 protein, it was possible to combine both motifs into a single molecule (**4**). In this way, the compounds first discovered that bound with mM affinity were optimized to a 10 μ M ligand suitable as a lead for further studies towards an antiviral agent for human papillomavirus.

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Emerging molecular targets

A key to Alzheimer's disease?

Marijuana

Researchers have known for a long time that the use of marijuana is associated with memory impairment. One striking feature of marijuana is that short-term memory, required for immediately recalling lists of objects, is badly hampered, whereas long-term memory, used for recalling past events and historic facts, is not affected. This situation is reminiscent of senile dementia, in particular Alzheimer's disease, except that the memory retention effects of mari-

juana use are completely reversible. It has also been known for some time that 9- Δ tetrahydrocannabinol, the active ingredient in marijuana, blocks long-term potentiation (LTP) in the hippocampus CA1 region of the brain, an area implicated in short-term memory processing.

2-Arachidonylglycerol

Recently, Dr Daniele Piomelli and coworkers at the Neurosciences Institute (San Diego, CA, USA) have identified an endogenous brain cannabinoid, 2-arachidonylglycerol (2-AG), which is produced in electrically stimulated brain slices in a tetrodotoxin-sensitive, calcium-dependent fashion, activates cannabinoid CB1 receptors, and prevents LTP at CA3/CA1 synapses [*Nature* (1997) 388, 773–778]. The original identification of 2-AG as an endogenous cannabinoid agonist was made in 1995 in the canine gut by Raphael Mechoulam and his colleagues from the Hebrew University (Jerusalem, Israel). The new study, however, embraces the required criteria for establishing the role of 2-AG as an endogenous brain neuro-modulator.

Biochemical synthesis

The identification of 2-AG as an endogenous brain cannabinoid follows the identification, several years ago, of the first endogenous brain cannabinoid ligand, anandamide. However, unlike anandamide, which is formed from phospholipids via the action of phospholipase D, 2-AG is formed from phospholipids via the more ubiquitous phospholipase C (PLC) pathway, employed by numerous G-protein-coupled neurotransmitter receptors. Several hor-

mones and peptides, such as thrombin and endothelin, also utilize the PLC pathway. This pathway crosslinks with the protein kinase C (PKC) signalling pathway, as its primary product, diacylglycerol (DAG), is both an activator of PKC and a precursor for 2-AG. Another PLC product, inositol 1,4,5-triphosphate, mediates Ca^{2+} release from intracellular stores, thereby affecting 2-AG production from DAG by the calcium-dependent DAG lipase.

Most notably, 2-AG reaches much higher brain levels, ~170-fold, than anandamide (~4 nmol g^{-1} tissue compared with 23 pmol g^{-1} tissue). The identification of 2-AG as the major endogenous brain cannabinoid agonist may thus herald a new route for designing memory-enhancing drugs. Indeed, selective CB1 antagonists, such as Sanofi Research SR141716A, were recently shown to possess distinct memory-enhancing properties [Terranova, J.P. *et al.*, *Psychopharmacology* (1996) 126, 165–172]. It remains to be seen whether 2-AG is elevated in memory-impaired individuals. However, the rapid turnover of 2-AG may prohibit human post-mortem studies (Piomelli's group used rapid freezing to measure brain 2-AG levels). Studies in animal models of Alzheimer's disease will ultimately be required to assess whether 2-AG has a plausible role in memory processing and memory impairment.

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Erratum

In the January Monitor section, the Profile article entitled *Antigene oligonucleotides* by Wentland, M.P. [*Drug Discovery Today* (1998) 1, 45] showed the structures of two nucleotide triplexes. These were incorrect and should have appeared as shown. We apologise to the author and the readers of the journal for this error.

