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Targets for chemical intervention: how natural products can provide leads for new CNS therapeutics

A. JACKIE HUNTER

SmithKline Beecham Pharmaceuticals, New Frontiers Science Park (North), Third Avenue, Harlow, Essex CM19 5AW

Natural products can provide targets for chemical intervention in four main ways which can be of benefit in the design of therapeutics for CNS disorders:

Directly acting as the therapeutic entity

Provision of novel chemical leads through natural product screening

Provision of tools for dissecting out pathways and mechanisms

Ethnopharmacological leads to new indications or new approaches

Historically, natural products have been successfully developed as useful CNS therapeutics, primarily for use as analgesics e.g. morphine and cocaine. Between 1983 and 1994 there were approximately 520 new drug approvals by the FDA and related agencies (Desmet 1997). Of these 520, 30 came directly from natural products and 173 were either semisynthetics or synthetics modelled on a natural product parent, although few of these were for CNS indications. However a number of companies are currently focused on developing natural product extracts specifically for CNS disorders e.g. Phytopharm (Alzheimer diseases and obesity) and Shire Pharmaceuticals (galantamine a cholinesterase inhibitor for Alzheimer's disease).

The rapid growth in robotics and assay technologies has allowed for the setting up of natural product screening groups which can screen hundreds of thousands of biologicals against a specific target. These biologicals may be microbiological fermentation broths or extracts from plants and animals. From this work has come a number of compounds for treating cancer, infection and cardiovascular disorders. In addition, leads which are of potential benefit in neurodegenerative disorders have also been found e.g. immunophilins and calpain inhibitors. Many companies are actively working in this area. For example, immunophilin derivatives such as GPI1046 have been shown to be neuroprotective in a number of animal models of neurodegenerative diseases.

Plant and animal extracts have also been a valuable source of tools for dissecting out basic physiological mechanisms. Plant extracts provided chemicals such as yohimbine and reserpine which were fundamental to the dissection of aminergic systems. More recently the venoms of sea snails (Conus sp.) and spiders have provided tools for the dissection of calcium and potassium channel pharmacology.

Ethnopharmacology can provide a more directed approach to screening and compound testing (Cott 1995). The observation that capsaicin, the extract from chilli peppers, was analgesic lead to the use of this compound, and related natural products such as resiniferatoxin, as a template for creating analogues (Szallasi & Blumberg 1996; Appendino & Szallasi 1997). Subsequently the vanilloid receptor has been cloned which could provide a target for chemical screening to obtain more novel chemical structures for testing as potential analgesics (Caterin et al 1997).

Thus natural products have provided the pharmaceutical industry with a rich source of chemical diversity from which both novel therapeutics and tools can be fashioned.

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