



Editorial

Plants and the central nervous system

This special issue of *Pharmacology, Biochemistry and Behavior* is dedicated to reviews and original research papers dealing with the effects of plants and their constituents on the central nervous system (CNS), particularly regarding behavioural aspects. It is difficult to know the baseline of human behaviour without regular doses of such plant extracts as tea, coffee, chocolate and inhaled volatiles from tobacco, because these are an integral part of life for almost everyone in the developed world and also in industrially developing communities. In addition, most cultures have their distinctive plants, which are used in a social or religious context as well as in the diet. Such use cannot strictly be described as medicinal, because the plants are not being used to treat an illness or prevent a disease, but more as a way of enhancing the quality of life, by increased social interaction, or as an escape from the negative aspects of life, by reducing or even eliminating their effect for a period. It is somewhat ironic that plants and their extracts belonging to the latter category cause many problems as drugs of abuse in industrialised societies where, on the material level, many users “have never had it so good.” Thus, cocaine, opium and heroin abuse are the cause of many problems in society, whilst the widespread use of tobacco, used largely for its effects on the CNS, is a serious drain on healthcare resources. Cannabis use is very widespread in spite of severely restrictive legislation in many countries, and whilst the extent and nature of its detrimental effects on individuals and society are hotly debated, there is common agreement that it affects the CNS. The endogenous cannabinoid system seems to be present since early stages of life, and cannabinoid exposure during development produces long-term neurobehavioural effects. The effects of perinatal exposure to cannabinoid are described in the papers by Moreno et al. and Gonzalez et al.

It should be noted, however, that it is only dosage and usage separate problems and benefits for a particular plant or its products in many situations and that many such “problem plants” yield compounds that provide useful pharmaceuticals. Many analgesics have been derived from morphine from opium, whilst cocaine has provided a template for effective local anaesthetics. Interesting work is in progress on the therapeutic possibilities of using cannabis to reduce severe pain in diseases such as multiple sclerosis and cancer, and other therapeutic possibilities of

the use of compounds derived from cannabis constituents are discussed in the paper by Diana et al.

Most of the papers in this special issue are concerned with plants and their constituents, which could be classed as pharmaceuticals, i.e., for the alleviation or cure of an illness. In recent years, the use of substances to prevent illness developing has received much attention, and healthcare appears to be increasingly focussed on the preservation of “wellness” as well as the treatment of illness.

Rational treatment of CNS disorders by plant materials is in its infancy due to the complex chemistry and organisation of the CNS and also to the complex chemistry and pharmacology of a plant extract, which may contain a bewildering variety of chemical compounds. Detailed knowledge of both of these factors has become available only fairly recently, but clues to plants worthy of investigation are provided very often by the study of plants used traditionally in traditional medicine, as poisons and in religious rituals, a discipline named ethnopharmacology. The means by which the human race found the medicinal properties of such plants is a fascinating but unanswerable question, but the long history of such uses cannot be denied, albeit on an empirical basis, and it is only now that the chemical and mechanistic bases for use are being uncovered. The review by Carlini gives an introduction to some of these, whilst that by Howes and Houghton concentrates particularly on plants used for improvement in age-related impairment of memory and cognition by Ayurveda and Chinese medicine, the two oldest major sophisticated systems of medicine practised in the world. Butterweck et al. provide some insight into the mode of antidepressant action of *Apocynum venetum* leaves, used in traditional Chinese medicine, whereas Watanabe et al. investigate the antidementia effect of Choto-san, a mixture of medicinal herbs, traditionally used in Chinese/Kampo medicine. The two papers by Jain et al. and Bhattacharya and Muruganandam are being more focussed on single species like *Clitoria ternatea* and *Withania somnifera*, respectively, from the Ayurvedic tradition. In these papers, modern pharmacological findings, which support traditional uses, are discussed and a similar treatment is applied to plants from less well-known cultural traditions in the paper by Elisabetsky's group on the Brazilian plant *Ptychopetalum olacoides* and by Schwarz et al. on *Banisteriopsis caapi*, originating from the Amazonian part of Brazil and neighbouring countries.

It should be noted that plants have played an important part in the development of neurotransmitter pharmacology, particularly in those compounds that are important for understanding CNS function and dysfunction. Many of these compounds have an agonist or antagonist effect on receptors and contain pharmacophores analogous to endogenous compounds. Thus, ephedrine from the Chinese drug *Ma Huang* (*Ephedra sinica*) was recognised over 70 years ago to have a pharmacological activity and chemical structure similar to the endogenous adrenaline and dopamine. Physostigmine from Calabar beans *Physostigma venenosum*, a Nigerian ordeal poison, was a key molecule in understanding the role of acetylcholine as a neurotransmitter because it inhibits choline esterase, thus prolonging the cholinergic response at the receptor by maintaining active concentrations of acetylcholine. In recent years, this activity has been exploited in the treatment of symptoms of Alzheimer's disease, because patients with Alzheimer's disease have been shown to have low levels of acetylcholine. Several plant constituents have been found to have this effect, and some clinical work is in progress with both natural products and their derivatives. The papers by Tildesley et al. and Perry et al. on Spanish sage (*Salvia lavandulaefolia*) are a welcome addition, giving clinical consolidation to the cholinesterase inhibitory activity. Another paper on sage oil by Savelev et al. demonstrates the interactions between the constituents and emphasises the fact that activity of an extract, both qualitative and quantitative, cannot be extrapolated too closely from the activity of one constituent because of synergistic or antagonistic effects.

In many medicinal plants, especially those with potent effects at small doses, the activity can be ascribed mostly to a single active ingredient, which was comparatively easy to isolate. Such compounds were discovered over 100 years ago. Where active compounds have been identified, they may be developed as drugs, as has happened with the cholinesterase inhibitor galantamine, but are often rather used as templates for the design of other molecules. Such derivatives retain the desired activity but have additional attractive features such as enhanced activity or reduced toxicity. Nabilone, derived from cannabis constituents, is the subject of the paper by Diana et al., whilst the paper by Zangara concerns a derivative of Huperzine from the Chinese clubmoss *Huperzia serrata*.

However, there are many other traditional medicinal plants with a reputation for affecting behaviour, cognitive function and other CNS-related activities where it has been difficult to identify one particular compound, or even one class of compounds, as responsible for the observed effects. The overall effect may be the result of a combination of different activities due to different types of compounds, and there may be the added complication that the effect may only be significant after a considerable period of treatment and may be difficult to quantify. Some such plant materials have been widely sold and used in

recent years in the West, and the papers on Ginseng and *Ginkgo biloba* by Kennedy and Scholey, Kennedy et al. and Hartley et al. deal with these products. Of particular interest is the paper by Marder et al., concerning *Valeriana* species and the benzodiazepine receptor binding activity of the flavonoids. *Valeriana officinalis* is well established as a herbal anxiolytic and tranquiliser in Europe, and related species are used for similar purposes in many other traditional medical systems. Clinical evidence supports this traditional use, but the identity of the compounds responsible is still not clear. In fact, several different compound types present have been shown to have effects that could contribute, but Marder's studies are the first to emphasise the important role that the flavonoids might play.

There has been much interest and debate in the last two decades into the relationship between diet and health. Whilst most studies have been concerned with the preventive aspects of foodstuffs against cancer or cardiovascular disease, there is some evidence that the function and health of other major body systems might also be affected. The paper on soya intake and cognitive function in postmenopausal women (Duffy et al.) is an interesting case in point.

Unfortunately, addiction is a common aspect of modern Western civilisation. In addition to the great costs incurred from its social effects, its treatment also devours large amounts of resources in financial and human terms. The most common addiction is probably to alcohol, and plant-derived treatments for alcoholics form the basis of the papers by Rezvani et al. and Overstreet et al. Constituents from an African plant *Tabernanthe iboga* have aroused some interest because of claims that they are useful anti-addictive agents, and the paper by Maisonneuve and Glick presents data dealing with the activity and potential use of one of these alkaloids.

The hallucinogens are a special class of plants belonging to the strictly nonmedical category, which alter the perception of space and time and other interactions with the environment. They are frequently used individualistically or collectively for hedonistic purposes, although in some societies they are used in religious rites to gain access to the spiritual world and sometimes to divine the causes of disease. Hallucinogens have been the subject of several learned texts and research papers, and their chemistry is well studied, even if the mechanism of action is far from clear. No papers are included that deal specifically with this interesting class of substances, but they are discussed to some extent in the review by Carlini.

The themes of the papers, which have been accepted for this special issue, illustrate the diversity in studies of plants and the levels of study encompassing molecular pharmacology through animal and clinical studies on compounds and extracts to behavioural and epidemiological approaches. Inevitably, there are important groups and topics

that are not represented, but it is hoped that this collation will stimulate further interest on the part of scientific investigators into this fascinating area with which most of the human race has been involved since before the dawn of history.

Peter J. Houghton
*Department of Pharmacy, King's College London,
Franklin-Wilkins Building, 150 Stamford Street,
London SE1 9NN, UK*
E-mail address: peter.houghton@kcl.ac.uk

Pallab Seth*
*Psychopharmacology Research Unit,
Centre for Neuroscience Research,
GKT School of Biomedical Sciences,
King's College London, Hodgkin Building,
Guy's Campus, London SE1 1UL, UK*
E-mail address: pallab.seth@kcl.ac.uk
Tel.: +44-207-848-6668; fax: +44-207-8486660

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* Corresponding author.