

Trends in Pharmacological Sciences

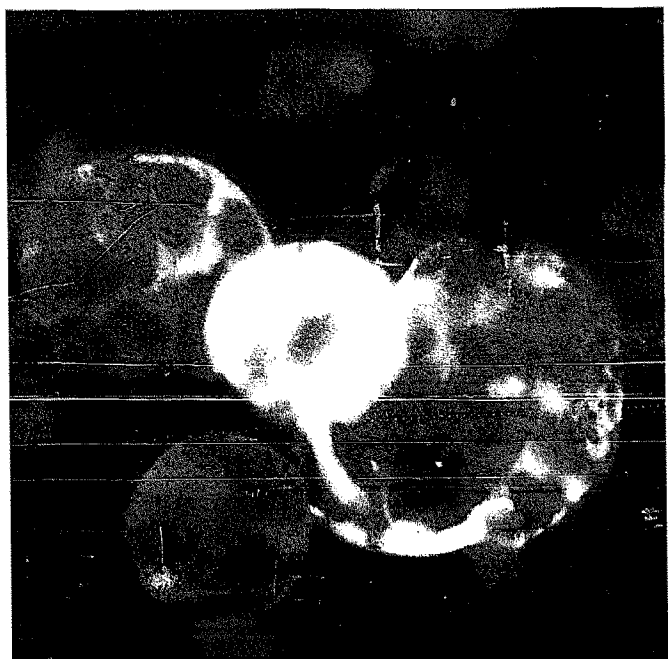
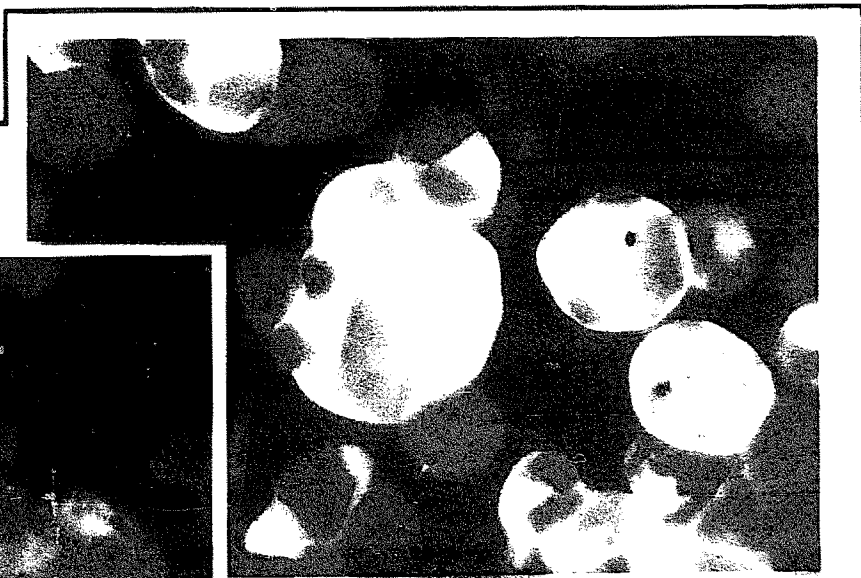
including TOXICOLOGICAL SCIENCES

PCP-NMDA connection provides hope in cerebral ischemia but new direction for antipsychotics

IT WAS AT the first French-US seminar on phencyclidine (PCP), held in Montpellier, France in 1983, that scientists interested in excitatory amino acids brought to the attention of those involved in PCP research that PCP was a potent, specific antagonist at the *N*-methyl-D-aspartate (NMDA) subclass of glutamate receptors. Since that connection was made, research into the mechanism of

action of PCP and its congeners has taken a dramatic and fascinating turn, enhanced by, as well as enhancing, the explosion of knowledge about the NMDA receptor itself (Ref. 1).

Much of the data and discussion at the recently-held second seminar on PCP and related compounds* centered around PCP as an NMDA antagonist. Striking neuroanatomical overlap between PCP binding sites and NMDA receptor sites, as well as similar behavioral effects of PCP and other NMDA antagonists supported electrophysiological data: some PCP-like compounds appear to block the NMDA-associated ion channels when they are in an open state, i.e. when they are activated by glutamate or glutamate-like substances. The noncompetitive nature of PCP



Is drug therapy for AIDS an attainable goal?

antagonism of NMDA suggests that PCP and the endogenous excitatory amino acid do not share the same receptor, but interact in an allosteric manner; the PCP binding site may be located within the NMDA-activated ion channel.

Channel localization of the PCP binding site could dash hopes of developing an antipsychotic agent that acts via antagonism at the PCP binding site. If PCP action is through its physical presence within an ion channel, it is likely that any drug that bound at this site would have PCP-like properties. Ever since the identification of PCP binding sites, drug development programs have been scrambling to synthesize a drug that binds to this site but has no functional activity. Such an antagonist would have potential for treating schizophrenia, since PCP itself produces symptoms very much like those of schizophrenia in some people who abuse it. Data presented at the current meeting indicated that, although compounds from as many as six different chemical classes bind to the PCP site, and small structural alterations in active compounds from each of these classes results in marked loss of binding affinity, all drugs that bind are either active as PCP-like compounds or they have limited access to the CNS - no PCP antagonist has yet been found. Thus, even negative data tend to support the notion of an ion channel binding location for PCP.

**The Second US-French Sponsored International Seminar on Sigma Opioid Phencyclidine-like Compounds as Molecular Probes in Biology, Ann Arbor, MI, June 29-July 2, 1987.*

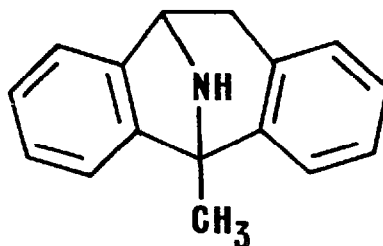
Front cover picture

Left: HIV antigen expression in MT4 cells determined by indirect immunofluorescence with polyclonal antibodies, counterstained with Evans blue. Note typical giant cell formation.

Right: The same cells photographed 4 days after HIV infection of the cells.

Photos supplied by Eric De Clercq. See p.339.

However the NMDA-PCP connection may be taking clinical investigators into another, equally exciting, therapeutic direction - that of protection against the damage produced by cerebral ischemia. As described by Dr D. W. Choi (Stanford), the neurotoxic effects of excitatory amino acids *in vitro* is well known, and the lack of such toxic effects in the normal brain may be due to endogenous amino acid sequestration systems.



MK-801

When these protection systems break down, as may occur during cerebral ischemia, release of glutamate, perhaps primarily through action on NMDA-sensitive sites, leads to Ca^{2+} entry and cell injury, which in turn leads to further release of glutamate. This cascade effect may be related to the 'maturation' aspects of cerebral ischemia, in which damage continues to occur several hours following the ischemic episode. The developing nature of the pathology suggests that appropriate intervention following the episode has a chance to reduce the severity of the sequelae. In Dr Choi's model of murine cortical cell cultures, the PCP-like drug (+)-SKF 10047 (N-allyl-normetazocine) protected against both early and late developing cell injury produced by application of NMDA or by hypoxia.

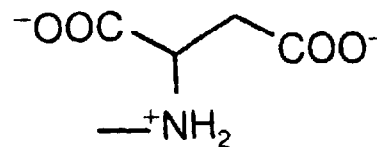
Dr L. L. Iversen (Harlow, UK) described the effects of MK-801 [(+)-5-methyl-10,11-dihydroxy-5H-dibenzo(a,d)cyclohepten-5,10-imine], a non-competitive NMDA antagonist with biochemical and behavioral properties in common with PCP, in protecting against the damage produced by excitatory amino acids in several *in-vivo* models. High doses of MK-801, delivered prior to temporary (5 min) bilateral carotid occlusion in Mongolian gerbils, produced virtually complete protection against cellular damage,

which was most profound in the CA1 area of the hippocampus, an area rich in NMDA-type glutamate receptors.

Although other agents, such as anticonvulsants and Ca^{2+} channel blockers, can have neuroprotective effects in some models when given prior to injury, MK-801 was effective in the gerbil model, showing 50% of its maximum protective effects, when given even 24 hours following the ligation. Thus, this agent may be able to prevent some of the damage resulting from the cascade of glutamate release following ischemia.

Dr M. V. Johnston and his group (Ann Arbor) reported on the effects of several agents on neuronal damage produced by combination of unilateral carotid ligation and hypoxia in seven-day-old rats. Although competitive NMDA antagonists such as 2-APH (2-amino-7-phosphoheptanoic acid) did not have any protective effects even when administered *i.c.v.*, MK-801 was able to afford complete protection if administered at the onset and 75 min after hypoxia.

The possibility that PCP-like agents may have some utility in dealing with neurodegenerative disorders, as well as in cerebral ischemia, was hinted at by Dr A. B. Young (Ann Arbor) who pointed out that, as with ischemia, Alzheimer's disease seems to affect the CA1 neurons of the hippocampus more than other



NMDA

areas. There is a 40% reduction in binding of PCP-like drugs and NMDA in the brains of Alzheimer's patients. Some relation between neurodegenerative disorders and excitatory amino acids appears possible, but remains to be worked out.

Also among the promising, but as yet poorly understood, areas of PCP research is that related to the σ receptor. As described in the November 1986 issue of *TIPS*, PCP has recently been found to bind

with lower affinity to a second site². Other drugs that attach to this site include SKF 10047, for which the site is named, haloperidol, pentazocine, cyclazocine, and ditolylguanidine. Identification of a function for this binding site has been hindered, in part because most of the drugs that bind here have actions that can be attributed to actions at other sites. Most of the effects of SKF 10047 are due to interaction at PCP sites, and the effects of haloperidol can be related to its effects at dopamine receptors. As might be expected under such circumstances, drugs that bind to the σ site have few actions in common. Dr S. W. Tam (Wilmington) reported on a discriminative effect of low doses of (+)-SKF 10047 and of (+)-pentazocine that appears to differ from that produced by PCP. Haloperidol acts as an antagonist of these effects. The possibility that it is the σ site that mediates the psychotomimetic effects of PCP and SKF 10047, raises the hope that development of antagonists of this, rather than the

PCP site, can result in development of a better antipsychotic agent.

Terminology

A committee on nomenclature at this meeting accepted the feelings of the attendees and recommended that the term PCP be used to refer to actions of drugs that are like those of PCP and probably related to NMDA antagonism. The term σ should be used to refer to drugs that bind to the high affinity (+)-SKF 10047 site which has a distinct localization from that of PCP. The function of binding to the σ site has not been determined and a prototypic agonist or antagonist has not yet been identified. In the future, the term opiate will not be applied to this particular σ site. A report from this committee is forthcoming.

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The oral presentations and posters of the seminar, as well as the discussion of issues raised by speakers, will be published later in the year by NPP Books, PO Box,

1491, Ann Arbor, MI 48106. Abstracts of the papers and posters will appear in the September issue of *Pharmacology, Biochemistry and Behavior*.

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References

- 1 Special issue (1987) *Trends Neurosci.* 10
- 2 Manallack, D. T., Beart, P. M. and Gundlach, A. L. (1986) *Trends Pharmacol. Sci.* 7, 448–451

AWARDS

A. J. Clark Award

The first A. J. Clarke Studentship has been awarded by the British Pharmacological Association to Ms Carol Nadin who will work with Dr J. M. Edwardson in Cambridge, UK on protein insertion into plasma membranes in epithelial cells.

CURRENT AWARENESS

The pathogenesis of the amnesia of Alzheimer's disease

Alzheimer's disease is a complex progressive dementia that begins insidiously in late middle age or old age, and is characterized by amnesia, apraxia, language and cognitive disturbances, and an impairment of spatial perception. Symptoms progress in the course of years to severe deterioration. Pathological changes include cortical atrophy, enlargement of the ventricles, senile plaques (round foci of enlarged neurites, abnormal dendrites, amyloid, astroglia and microglia), and neurofibrillary tangles (intracellular fibrillary occlusions) (Fig. 1). The pathological changes are not pathognomonic: they are also seen in healthy old humans, in old monkeys, or in patients with other forms of dementia¹. However, if these changes are profuse enough in the post-mortem examination of a patient with a severe dementia of the type mentioned above, they are considered diagnostic.

The pathogenesis of the amnesic syndrome of Alzheimer's disease has been widely discussed in recent years. For a long time, the prevalent hypothesis was that the amnesia of patients with 'senile dementia of the Alzheimer type' (SDAT) was due to a dysfunction of the brain cholinergic system^{1–3}. Evidence for this was either indirect (scopolamine induces retrograde amnesia in rats and humans, physostigmine sometimes has an opposite effect, physostigmine is sometimes fleetingly effective in improving memory scores in SDATs^{1,3}), or circumstantial (neurofibrillary tangles, and cell loss, are seen in the cholinergic nucleus basalis of Meynert in SDATs^{4,5}); senile plaques are seen both in this region and in cortical projections of basal cholinergic neurons^{6,7}.

However, neurofibrillary tangles in SDATs are also found in the medial basal hypothalamus⁸, which is

the site of the β -endorphinergic nucleus of the brain⁹; in the locus coeruleus⁸, which is the noradrenergic nucleus; in the raphe⁸, the site of serotonergic cell bodies; in the hippocampus, amygdala, and neocortex⁸, which receive projections of these three and many other systems as well. Senile plaques are observed not only in the neocortical projection sites of cholinergic neurons^{6,7}, but also in non-cholinergic neocortical projections¹⁰, in the amygdala, hippocampus, and other regions¹; and, as previously mentioned, in old people with no SDAT symptomatology, or in patients with other forms of dementia¹.

This led some investigators to formulate alternative hypotheses to explain the amnesia of Alzheimer's disease. Indeed, in recent years, several authors have reported reductions in the levels or turnover of brain nor-epinephrine, dopamine and 5-HT^{11,12}, or in the CSF level of somatostatin, substance P¹² or β -endorphin¹³, in SDATs. A problem with the biogenic amine studies is that they also provide only circumstantial evidence: similar changes occur in old patients without SDAT symptomatology¹¹.