SYMPOSIUM SESSIONS

Cross-Cultural Perspectives on Somatoform Disorders

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This paper will address the following issues pertinent to understanding the expression of somatic symptoms in different cultures:

(i) clinical approaches to interpreting patients' somatic complaints;

(ii) linguistic variation in available terms and phrases used by lay people to describe somatic symptoms; and

(iii) types of somatic complaints observed in patients.

Cross-cultural patterns and variation in these three domains will be described on the basis of reports in the literature and data collected in the WHO International Study of Somatoform Disorders.

Validity and Reliability of Procedures for the Assessment of Somatoform Disorders

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The WHO Mental Health Programme has developed several diagnostic interview questionnaires for the reliable and valid assessment of mental disorders. The CIDI is one such tool that has already been field-tested in more than 20 countries throughout the world. It has demonstrated good reliability and acceptability for cross-cultural studies. The Somatoform Disorders Schedule (SDS) is a newly-developed instrument based largely on the CIDI 1.1 section on somatoform disorders. It has been field-tested in five culturally distinct locations (USA, Brazil, Italy, India and Zimbabwe) and has been found to have high inter-rater reliability as well as test-pretest diagnostic reliability. Interviewer-observer reliability was also assessed, as were "inter-site" comparisons, and revealed a high reliability coefficient. This instrument should prove to be a useful instrument for future research on somatoform disorders.

ELIPRODIL: A NOVEL NEUROPROTECTIVE AGENT ACTING AT A MODULATORY SITE OF THE NMDA RECEPTOR.

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The NMDA receptor, composed of heteromeric assemblies of NR1 and NR2 (A-D) subunits, is co-activated by glutamate and glycine and positively modulated by spermine and spermidine via at least two modulatory polyamine sites with distinct actions. Polyamines increase glycine site affinity but also increase NMDA responses in the presence of saturating concentrations of glycine. The piperidine-ethanol derivatives ifenprodil and eliprodil have been shown to block the NMDA receptor via an interaction with a modulatory polyamine site. They partially displace [^{3}H]CPP, [^{3}H]glycine or [^{3}H]MK801 at submicromolar concentrations but antagonize the stimulatory effects of polyamines on the binding of these ligands. In different brain areas, their NMDA antagonistic effects have been shown to be total, biphasic or partial and can be reversed either by the polyamines or by glycine, suggesting action at the polyamine site that regulates glycine site affinity. [^{3}H]ifenprodil or eliprodil label a site on the NMDA receptor which is totally displaced by spermine and spermidine in a competitive manner. Recent studies have shown that ifenprodil and eliprodil selectively antagonize a specific NMDA receptor subtype . In transfected Xenopus oocytes ifenprodil antagonises NR1A/NR2B receptors with high affinity (IC_{50}=340nM) in a glycine reversible and voltage-independent manner and blocks the NR1A/NR2A subtype (IC_{50}=146μM) in a voltage-dependent and glycine-insensitive manner (Williams, Mol.Pharmacol. 44, 851-859, 1993). The selectivity of ifenprodil for a subtype of NMDA receptor is supported by the distribution of polyamine-sensitive [^{3}H]ifenprodil binding sites which closely matches that of NR2B receptor mRNA. In striatal slices, ifenprodil and eliprodil block the stimulatory effects of NMDA on

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acetylcholine release, but are without effect on NMDA evoked spermidine release. This profile is shared by magnesium, polyamine spider toxins and the relatively less psychostimulant NMDA channel blockers dextrorphan and dextromethorphan while dizocilpine, phencyclidine, CGP37849 and L-689,560 block both responses with equal potency. Finally, in immature rat cerebellar Purkinje cells, dizocilpine, 2APV and 7-Chlorokynurenate totally block NMDA-induced calcium entry, which is however only partially blocked by ifenprodil or eliprodil.

Ifenprodil or Eliprodil protect against the neurotoxic effects of NMDA receptor activation in vitro; their protective effects in cortical culture can be reversed by spermine or spermidine. Eliprodil has been shown to be neuroprotective in mouse (ip,po), rat (po) and cat (iv) models of focal ischaemia and also provides extensive neuroprotection in a rat model of cerebral trauma. The window of therapeutic opportunity in the mouse focal ischaemia model is from 2-4hrs post-occlusion and considerably longer in cerebral trauma (~18hrs).

Antagonists at each other site of the NMDA receptor (channel, glutamate and glycine) have also been shown to exert neuroprotective effects in animal models of stroke or cerebral trauma. Unfortunately, NMDA receptor antagonism can be accompanied by a battery of undesirable side effects including, in varying degree, phencyclidine-like psychostimulation, amnesia, neurotoxicity, hypertension and tachycardia. These effects are particularly intense with certain NMDA channel blockers (although less so in the case of dextrorphan-like compounds), and can also be observed with competitive NMDA antagonists. Glycine antagonists appear to have a more favourable profile at neuroprotective doses, while eliprodil is completely devoid of such side-effects. The reasons for this favourable profile are likely to reside in its mechanism of action - antagonism of the effects of modulatory polyamines whose influence is increased in the ischaemic or traumatised brain. The fact that ifenprodil and eliprodil act at a specific NMDA receptor subtype, and that non-stimulant channel blockers also show a degree of native NMDA receptor subtype selectivity suggests that NMDA receptor subtype targetting could provide neuroprotective NMDA antagonists with a favourable therapeutic index.

Cholinesterase Inhibitors in Alzheimer's Disease

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Data generated to date by a number of large studies (Eagger et al, Davis et al, Farlow et al, and Murphy et al) indicate that aminoacridines, as a class of compounds, have a statistically significant effect to diminish, slightly, some of the cognitive symptoms of Alzheimer's Disease. The clinical significance of this acetylcholinesterase induced change is the central issue that will determine whether regulatory bodies will ultimately approve these agents. Clinical global improvement has been found in some of these studies, but not others. However, the possibility exists that patients have been underdosed, as a consequence of the potential hepatotoxicity that reflected in the elevation of transaminase levels that occur in a substantial number of patients. Nonetheless, higher doses of the amino acridines, if tolerated, might produce larger effects that would be more apparent to the clinician, or, alternatively, other cholinesterase inhibitors than aminoacridines that are devoid of the hepatic problems so far encountered might be administered in larger doses, particularly if they are relatively brain selective, to produce a level of enhancement of central cholinergic activity that would maximize symptom improvement.

There is little doubt that responsivity to cholinesterase inhibitors exists in only a subgroup of patients, and is robust in a further subgroup. Thus, a critical question is the biological substrate for the absence of efficacy of cholinesterase inhibitors in many Alzheimer's patients. One obvious explanation is that Alzheimer's disease is far more than simply a cholinergic deficit. Animal models have been utilized to address the heterogeneity of responsivity.

The efficacy of cholinesterase inhibitors to reverse the deficit in passive avoidance learning that is caused by a nucleus basalis lesion has been studied in animals in whom either a noradrenergic, serotonergic, or somatostatinergic deficit has been added to the cholinergic deficit. These data indicate that cholinomimetic compounds are just as efficacious in reversing the deficit in learning on a passive avoidance task following a nucleus basalis lesion when that lesion is combined with either a serotonergic or a somatostatinergic deficit. However, the combination of a noradrenergic lesion produced by either the injection of 6-hydroxydopamine or DSP-4 into the ascending noradrenergic bundle from the locus coeruleus, with a nucleus basalis lesion, completely obliterates the ability of a cholinergic compound to reverse the passive avoidance learning deficits. However, by combining drugs that enhance noradrenergic activity with those that enhance cholinergic activity it is once again possible to normalize the behavior of these animals with both noradrenergic and cholinergic deficiencies on passive avoidance learning tasks. Thus, these data encourage the use of drugs that will reverse multiple neurotransmitter deficits.