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EDITORIAL

GABA and acute psychoses[1]

Recent attempts to explain acute psychotic behaviour in terms of disordered cerebral neurotransmitter function have largely concerned the monoamines, serotonin, dopamine and noradrenaline (Crow, 1978). Most prominent among these endeavours is the dopamine hypothesis of schizophrenia, which in its current form proposes that the 'positive' symptoms of acute schizophrenia (or Schneider first-rank symptoms) depend on relative overactivity in certain dopaminergic pathways, most probably those in the mesolimbic system (Randrup & Munkvad, 1972; Carlsson, 1978; Van Praag, 1977). Support for this hypothesis is provided by evidence that the neuroleptic drugs which specifically diminish the positive symptoms of acute schizophrenia act at dopamine receptor sites to diminish the biochemical or physiological effects of dopamine. Studies of dopamine turnover in schizophrenic patients (Bowers, 1974; Post *et al.* 1975), or post-mortem studies of brain content of dopamine and its metabolites (Crow *et al.* 1979), do not show an increase in dopamine turnover for the brain as a whole or for specific regions in schizophrenia. However, post-mortem studies do indicate an increase in the dopamine content and in the number of dopamine or butyrophenone receptors in the mesolimbic system and striatum in the brains of chronic schizophrenic patients (Bird *et al.* 1979; Owen *et al.* 1978). These observations can be interpreted as showing diminished dopaminergic activity associated with the defect state of chronic schizophrenia (Chouinard & Jones, 1978; Mackay, 1980).

Alterations in the level of activity in any one neurotransmitter system may be the result or the cause of changes in the level of activity in other neurotransmitter systems. Physiological and pharmacological experiments have established a close interaction between dopaminergic and GABAergic pathways, particularly in the nigrostriatal system, but also in the mesolimbic system.

GABA-DEFICIENCY HYPOTHESIS OF SCHIZOPHRENIA

Focal injections of γ-aminobutyric acid (GABA) antagonists in mesolimbic structures (ventral tegmental area) in cats give rise to behaviour (arousal, searching, hiding, catatonia, staring and sniffing) reminiscent of schizophrenia (Stevens *et al.* 1974). These observations and other more theoretical considerations (Roberts, 1976) have led to the hypothesis that a relative deficiency of GABAergic activity within the mesolimbic and related systems is responsible for some features of the schizophrenic syndromes (Van Kammen, 1977). The dopaminergic neurons of the mesolimbic system (with cell bodies in the ventral tegmental area) are under a GABAergic inhibitory control (Wolf *et al.* 1978). Thus a GABA deficiency hypothesis can be complementary to a dopamine overactivity hypothesis of acute schizophrenia. Furthermore, pharmacological manipulations which enhance GABAergic function might be therapeutic in acute schizophrenia (Van Kammen, 1977).

Any generalized impairment of GABAergic function is associated with a lowered seizure threshold (Meldrum, 1975, 1979). The incidence of epilepsy is higher in schizophrenic patients than in the general population (Yde *et al.* 1941). This is largely attributable to the appearance of schizophrenic psychosis in some patients who have experienced complex partial seizures for several years (Slater *et al.* 1963; Flor-Henry, 1969). There is no evidence for a lowered threshold for generalized seizures in schizophrenic patients. A common, local, pathological process involving the temporal lobe and mesolimbic system could underly the coexistence of complex partial seizures and schizophrenia. The occurrence of spikes in depth electrode recordings from the septal regions in schizophrenic patients (Heath, 1954) is consistent with impaired GABAergic function within the mesolimbic system (Stevens *et al.* 1974).

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BIOCHEMICAL OBSERVATIONS

Cerebrospinal fluid (CSF) GABA content is reduced in epilepsy (Wood *et al.* 1979; Manyam *et al.* 1980). A preliminary report found normal GABA levels in untreated schizophrenic patients and reduced levels following neuroleptic therapy (Lichtshtein *et al.* 1978), but the methodology employed has been questioned (Hare *et al.* 1980). Gold *et al.* (1980) also found no difference between controls and schizophrenic patients. However, a recent report (McCarthy *et al.* 1981) described an increased CSF GABA content in patients with chronic schizophrenia.

Glutamic acid decarboxylase (GAD), the enzyme synthesizing GABA, was reported to be reduced in activity in the putamen, nucleus accumbens, amygdala and hippocampus of patients with chronic schizophrenia (Bird *et al.* 1977). This change was subsequently found to be largely or entirely dependent on the mode of death, a prolonged ante-mortem period of cerebral hypoxia, as in death from bronchopneumonia, being associated with a fall in GAD activity in deep brain nuclei (Bowen *et al.* 1976; McGeer & McGeer, 1979; Bird *et al.* 1979). Differences in GAD activity in the striatum, nucleus accumbens, or hippocampus are not found in a comparison of controls and schizophrenics who have died suddenly (Bird *et al.* 1979).

The mean brain GABA content of the nucleus accumbens and of the thalamus was originally reported to be reduced in brains from chronic schizophrenic patients (Perry *et al.* 1979). A subsequent report (Cross *et al.* 1979) found no difference in GABA concentration in the nucleus accumbens and thalamus compared with controls. A larger and more recent study finds small but significant decreases in GABA concentration in the nucleus accumbens and in the amygdala (Spokes *et al.* 1980).

In summary, available biochemical studies neither provide definitive evidence for the hypothesis of GABAergic deficiency in schizophrenia, nor do they disprove it.

PHARMACOLOGICAL STUDIES

Clinical pharmacological studies are all concerned with drugs which either directly mimic the action of GABA or enhance the action of endogenous GABA, since drugs which impair the inhibitory action of GABA are convulsant.

GABA agonists act at GABA receptor sites to reproduce the physiological actions of GABA. Thus there are at least as many different types of GABA agonist as there are types of GABA receptor. The latter can be defined by anatomical, physiological, pharmacological or biochemical procedures (Meldrum *et al.* 1980; Meldrum, 1981).

The classical physiological test system concerns post-synaptic inhibition (in the neocortex, cerebellum, hippocampus or spinal cord) which is bicuculline-sensitive and strychnine-insensitive, assessed at the single cell level with microelectrodes (Curtis, 1979). In this test system muscimol and various new synthetic compounds are potent GABA agonists; baclofen, 4-hydroxybutyrate and valproate are relatively inactive. There are also four or more different 'pre-synaptic' sites at which GABA may act to modify neurotransmission (Meldrum, 1981). Among these, the inhibition of primary afferent transmission in the spinal cord is the best studied. Pharmacologically, it is similar to GABA-mediated post-synaptic inhibition. There are also GABA sensitive 'autoreceptors' on GABAergic terminals (Mitchell & Martin, 1978); δ-amino-laevulinic acid is a potent agonist at this site (Brennan & Cantrill, 1979). In the peripheral autonomic nervous system and in the brain the release of monoamines can be inhibited by GABA and by baclofen (Bowery *et al.* 1980), through an action on a pre-synaptic receptor that is not bicuculline-sensitive. There is evidence for GABA-sensitive pre-synaptic receptors which influence the release of glutamate and aspartate (Gallo *et al.* 1981; Collins, 1980), but their pharmacology remains to be defined. There are also GABA receptors on axonal membranes which have been studied, using dorsal nerve root or cervical sympathetic ganglion preparations (Bowery & Brown, 1974; Brown & Marsh, 1978).

The physiological role of post-synaptic inhibition and of primary afferent pre-synaptic inhibition is partially understood, but the functional significance of other GABA receptors in the brain is

Table 1. *Acute psychotic symptoms following administration of GABA agonists or 'GABA-mimetics'*

Drug	Dose/day	Subjects	Symptoms	Authors
Muscimol	15 mg	Volunteer	Toxic psychosis	Waser (1967)
	5–10 mg	Schizophrenia	Worsening in confusion affect, thought disorder	Tamminga *et al.* (1978)
	5–9 mg	Tardive dyskinesia	Psychosis scores increased	Tamminga *et al.* (1979)
(δ-amino-laevulinic acid) Serine, glycine	2 mmol/kg	Porphyria	Depersonalization, dysphoria, visual hallucinations	Pepplinkuizen *et al.* (1980)
Baclofen	80–120 mg	Schizophrenia (chronic)	Worsening of schizophrenia (9/12)	Simpson *et al.* (1976)
	80–100 mg	Schizophrenia (acute)	Worsening of schizophrenia (3/4)	Davis *et al.* (1976)
	20–90 mg	Parkinson's disease	Toxic confusion, visual hallucinations	Lees *et al.* (1978)
	20–120 mg	Tardive dyskinesia	Confusional state	Gerlach *et al.* (1978)
4-hydroxybutyrate	1·5–5·25 g	Huntington's disease	Organic confusional state	McGeer *et al.* (1977)
Sodium valproate	750–3000 mg	Schizophrenia	Agitation, psychosis worse (6/8)	Lautin *et al.* (1980)
Amino-oxyacetic acid	2·7 mg/kg	Huntington's chorea	Acute psychotic behaviour (2/7)	Perry *et al.* (1980)
γ-acetylenic GABA	105–225 mg	Tardive dyskinesia	Confusion, time disorientation (2/10)	Casey *et al.* (1980)
	10–900 mg	Huntington's disease	Agitation, aggressivity, confusion	Tell *et al.* (1981)

totally obscure. The principal method for the study of their possible roles is the focal injection of GABA or GABA agonists in animal behavioural models. In certain such tests baclofen and 4-hydroxybutyrate, like muscimol, reproduce the effect of focal GABA injection (Olpe *et al.* 1977).

In man, GABA agonists and GABA-mimetics have been administered orally in a variety of experimental studies (see Table 1). Some of these studies were performed in patients with schizophrenia in the hope of identifying a therapeutic action either against acute psychotic symptoms (Tamminga *et al.* 1978; Lautin *et al.* 1980) or against the syndrome of tardive dyskinesia (Tamminga *et al.* 1979; Casey *et al.* 1980). As muscimol was known to be capable of inducing toxic psychosis in the normal volunteer (Waser, 1967), the exacerbation in psychosis scores found in schizophrenic patients was not unexpected. This exacerbation has been widely assumed to be a toxic side-effect of muscimol, not specifically related to its GABA agonist action. However, this effect should probably be considered in relation to the evidence for a worsening of psychotic symptoms in the majority of patients with acute or chronic schizophrenia treated with baclofen or with sodium valproate (Simpson *et al.* 1976; Davis *et al.* 1976; Lautin *et al.* 1980). In addition, several trials of these GABA-mimetics and of GABA-transaminase inhibitors which enhance brain GABA content (Meldrum, 1979; Palfreyman *et al.* 1981) in Huntington's disease or Parkinson's disease report the induction of an acute psychosis in a minority of patients (see Table 1).

A tentative interpretation of these clinical observations is that endogenous GABA in excess, true GABA agonists such as muscimol, or GABA-mimetics can all produce an acute psychosis by acting at a GABA receptor which has many of the features reported in studies of pre-synaptic GABA receptors. Interestingly, δ-amino-laevulinic acid, a potent, pre-synaptic GABA agonist, accumulates in porphyria. Loading with serine or glycine, the metabolic precursor of δ-amino-laevulinic acid, can precipitate a schizophrenia-like psychosis in patients with porphyria or related illnesses (Pepplinkuizen *et al.* 1980). The concentration of δ-amino-laevulinic acid in the CSF during an attack of

acute intermittent porphyria (Sweeney *et al.* 1970) is equivalent to that producing a 50 % inhibition of GABA release from synaptosomes through an autoreceptor effect (Brennan & Cantrill, 1979).

Among the clinical studies summarized in Table 1 only those concerning muscimol in schizophrenic patients (Tamminga *et al.* 1978, 1979) employed quantitative measures of specific schizophrenic symptoms. The majority of the cases reported conform to the pattern of acute toxic psychosis.

In summary, clinical studies with GABA agonists or GABA-mimetics show no therapeutic action against the positive symptoms of acute schizophrenia, and thus provide no support for a GABA-deficiency hypothesis of schizophrenia. By contrast, high doses of drugs known to act at GABA receptors other than the receptor responsible for post-synaptic inhibition are all capable of inducing acute psychoses, which vary from an apparent exacerbation of the schizophrenic syndrome in patients with acute schizophrenia to an organic confusional state in patients with a variety of neurological disorders. Thus an excessive local release of GABA, or hypersensitivity of a subgroup of GABA receptors, or an endogenous GABA agonist (such as δ-amino-laevulinic acid) might be responsible for some features of acute psychotic syndromes.

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