J Neural Transm (1991) [Suppl] 34: 203–210

Glutamate receptor antagonism: neurotoxicity, anti-akinetic effects, and psychosis

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Summary. There is evidence to suggest that glutamate and other excitatory amino acids play an important role in the regulation of neuronal excitation. Glutamate receptor stimulation leads to a non-physiological increase of intracellular free Ca^{2+}. Disturbed Ca^{2+} homeostasis and subsequent radical formation may be decisive factors in the pathogenesis of neurodegenerative diseases.

Decreased glutamatergic activity appears to contribute to paranoid hallucinatory psychosis in schizophrenia and pharmacotoxic psychosis in Parkinson's disease. It has been suggested that a loss of glutamatergic function causes dopaminergic over-activity. Imbalances of glutamatergic and dopaminergic systems in different brain regions may result in anti-akinetic effects or the occurrence of psychosis. The simplified hypothesis of a glutamatergic-dopaminergic (im)-balance may lead to a better understanding of motor behaviour and psychosis.

Introduction

It is only recently that excitatory amino acid receptors have been discovered. Through the use of selective agonists and antagonists it has become evident that these receptors consist of different subtypes (for review see Watkins et al., 1990). At present the most useful classification provides the following excitatory amino acid receptor subtypes: N-methyl-D-aspartate (NMDA) receptors, kainate receptors, quisqualate receptors or α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors, metabotropic receptors and L-aminophosphonobutyrate (L-AP4) receptors. Some important features of these excitatory amino acid receptor subtypes are given in Table 1. It is evident that these receptors fulfill a variety of different physiological functions depending on their regional and subregional location, their pre- or postsynaptic localization, the neurotransmitter system at which they are located and their quantitative distribution.

Table 1. Glutamate receptor subtypes: major pharmacological profile and localization

Glutamate receptor subtype	Agonist	Antagonist	Modulating system	Ionic channel	Localization
NMDA	NMDA L-aspartate L-glutamate	PCP Ketamine MK-801 SKF-10047 Mg^{++} N.C. CPP D-AP5 CGS 19755 DAA C.	polyamines glycine + D-serine + MNQX − 7-chlorokynurenate HA 966	Na^+ K^+ Ca^{2+}	postsynaptic
AMPA	quisqualate AMPA glutamate	CNQX NBQX DGG GDEE babiturates philanthotoxin		Na^+ Ka^+	postsynaptic, glial
Kainate	kainate, domoate				presynaptic
L-AP4	L-AP4 L-serine-O-phosphate				presynaptic
Metabotropic	quisqualate, ibotenate ACPD	L-AP3 L-AP4		NO coupling to PLC-system and via IP_3 influences intracellular Ca^{2+} stores	postsynaptic, glial

Abbreviations: *C.* competitive; *N.C.* non-competitive; *ACPD* 1-amino-cyclopentane-1, 3-dicarboxylic acid; *AMPA* α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; *D-AP5* D-2-amino-5-phosphonopentanoic acid; *L-AP3* L-amino-3-phosphonopropionic acid; *L-AP4* L-2-amino-4-phosphonobutanoic acid; *CGS 19755* 4-phosphonomethyl-2-piperidinecarboxylic acid; *CNQX* 6-cyano-7-nitroquinoxaline-2, 3-dione; *CPP* (±)-2-carboxypiperazine-4-yl-propyl-1-phosphonic acid; *DAA* D-aminoadipate; *DGG* D-glutamylglycine; *GDEE* glutamic acid diethyl ester; *HA 966* 1-hydroxy-3-amino-pyrrolidin-2-one; *MK801* (+)-5-methyl-10, 11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine maleate; *MNQX* 6,8-dinitroquinoxalinedione; *NBQX* 6-nitro-7-sulphamobenzo[f]quinoxaline-2,3-dione; *NMDA* N-methyl-D-aspartate; *NO* nitric oxide; *PCP* phencyclidine; *SKF-10047* N-allyl-normetazocine; + activating; − inhibiting

NMDA receptors are involved in the regulation of intracellular free Ca^{2+}-concentrations. It has therefore been suggested that glutamate and other excitatory amino acids play an important role in the regulation of neuronal excitation and may bring about neuronal destruction if administered in sufficient excess.

Glutamate toxicity and neurodegeneration

The regulation of Ca^{2+} and its compartmentalization is important for both presynaptic and postsynaptic events. Alterations in the extracellular/intracellular Ca^{2+} ratio can produce deleterious changes in cell function.

Altered Ca^{2+} homeostasis may influence a variety of physiological cell functions including Ca^{2+} transport systems, Ca^{2+} binding proteins and Ca^{2+}-activated proteases (Gibson and Peterson, 1987). A non-physiological increase of intracellular free Ca^{2+} leads therefore to a dysregulation of membrane-dependent processes. This is generally accompanied by a loss of energy supply to the cell, and the loss of ATP in particular alters the biochemical homeostasis of the cell.

Neurodegeneration is caused or accompanied by Ca^{2+} influx and intracellular Ca^{2+} mobilization. It has been suggested that excitatory amino acids play an important role in excitatory neurotoxicity and neurodegeneration (for review see Meldrum and Garthwaite, 1990). Glutamate with its high concentration in the mammalian brain is the probable neurotransmitter at most excitatory synapses and the most likely excitatory amino acid toxin. NMDA receptor channels permit a large Ca^{2+} influx and there is evidence to suggest that toxic Ca^{2+} entry occurs mainly through these channels (Garthwaite and Garthwaite, 1987). The activation of proteases and other Ca^{2+}-dependent enzymes such as protein kinase C, phospholipases and Ca^{2+}-calmodulin-dependent protein kinase II may contribute to glutamate toxicity (Meldrum and Garthwaite, 1990). The substantial increase of Ca^{2+}-activated proteases such as calpains causes destruction of microtubules, neurofilaments, etc. and may induce derangement of structural membrane integrity. Calpains also convert xanthine dehydrogenase to xanthine oxidase and free radicals are subsequently generated during purine metabolism. Increased phospholipase activity results in the release of lipids and leads to production of arachidonic acid, which can be metabolized to produce free radicals. Radicals increase lipid peroxidation of membrane constituents and enhance the release of excitatory amino acids. In addition, arachidonic acid blocks the uptake of glutamate into glial and neuronal cells.

All of these pathological events cause a catabolic state in which nutritional supply decreases. Neuronal processes are eventually destroyed and neurodegeneration becomes uncontrolled and progressive. In Parkinson's disease and in Alzheimer's dementia a loss of about 70% of cell bodies in the substantia nigra pars compacta and the nucleus basalis Meynert, respectively, is necessary before the major clinical symptoms are observed. Whether or not disturbed Ca^{2+} homeostasis and radical formation are

decisive pathobiochemical factors in these disorders is the subject of intensive research.

There is experimental evidence to suggest that excitotoxic mechanisms contribute to neuronal loss occurring as the result of cerebral ischaemia (for review see Meldrum and Garthwaite, 1990). Current knowledge suggests that a loss of glutamatergic function is a plausible hypothesis for the occurrence of productive symptoms in schizophrenia (see below). Decreased glutamatergic function may in theory be accompanied by a reduced rate of cerebral infarction in patients with schizophrenia. In order to examine this proposition we took an unselected series of 880 patients with neurological or psychiatric diseases who died at Lainz Geriatric Hospital, Vienna, between 1981 and 1988. In addition to routine autopsy, examinations were performed by a neuropathologist (K. J.). The number and percentage of patients dying of cerebral infarction was determined for the various diagnoses (Table 2). The number of such deaths was highest in the group of patients with a history of cerebral infarction. In contrast to neurological diseases, psychiatric disorders showed the lowest death rate caused by cerebral infarction. This preliminary evaluation is in line with the theories of decreased glutamatergic activity in schizophrenia and enhanced excitatory amino acid release in patients with cerebral infarction. It is interesting to note that cerebral infarction was not found in a group of 40 depressed patients. It is not known whether this can be directly related to decreased glutamatergic activity or to antidepressant therapy which may antagonize NMDA receptor function (Reynolds and Miller, 1988).

Table 2. Neurological and psychiatric patients dying of neuropathologically confirmed cerebral infarction (1981–1988)

Disease	Patients (n)	Sex F/M	Age (n) <65 years	>65 years	Presumed NMDA receptor density	Cerebral infarction as cause of death N	%
Cerebral infarction	77	48/29	13	64	↑ ↓	21	27
Dementia + cerebrovascular insufficiency	522	313/209	58	464	↑ = ↓	52	10
Parkinson's disease	34	21/13	4	30	↑ ↓	3	11
Other neurol. disorders (Huntington's disease, multiple sclerosis)	45	18/27	25	20	↑	9	20
Dementia of Alzheimer type	64	6/58	45	19	↑ ↓	3	5
Schizophrenia	105	66/39	45	60	↓	1	1
Depression	40	29/11	7	33	?	0	0

NMDA receptor densities are presumed to be increased (↑), decreased (↓) or unaltered (=) in comparison with control subjects. Increased, decreased or unaltered pathway activity may occur in the same disease depending on the loop systems involved. The quantity of change, however, is dependent on the progress and duration of the disease. This information is not given here

The role of glutamate in schizophrenia

It has recently been postulated that decreased glutamatergic function is a pathobiochemical marker of schizophrenia (Kim et al., 1980). A decreased release of glutamate has been found in the frontal and temporal cortex of schizophrenic patients (Sherman et al., 1991) while increased NMDA receptor density has been measured in the temporal and parietal cortex (Suga et al., 1990). In the putamen, increased (Kornhuber et al., 1989) and unaltered (Suga et al., 1990; Weissman et al., 1991) NMDA receptor densities have been reported. Quisqualate receptors are not changed in the frontal, temporal and parietal cortex (Kurumaji et al., 1990) while kainate receptor binding is increased in the frontal cortex (Deakin et al., 1989; Nishikawa et al., 1983) and not changed (Deakin et al., 1989) or decreased (Kerwin et al., 1988; Harrison et al., 1991) in the hippocampus. Taken together, the data available is of value only as a starting point for further research since both the number of studies and the number of brain regions examined are limited. For example, the most vulnerable brain regions in schizophrenia, the entorhinal cortex (Jakob and Beckmann, 1986) and the prefrontal cortex (Benes et al., 1986), have not been studied in detail and only preliminary biochemical evidence exists to suggest that NMDA receptor density is marginally increased in the entorhinal cortex (Kornhuber et al., 1989).

We assume that it is the loss of glutamatergic activity that induces an enhanced dopaminergic tone. The "dopamine hypothesis" of schizophrenia suggesting dopaminergic overactivity in the pathobiochemistry of some productive symptoms (paranoid hallucinatory psychosis) seems to be valid according to this assumption (Kornhuber et al., 1990).

Anti-akinetic effects of glutamate antagonists and pharmacotoxic psychosis

In Parkinson's disease enhanced glutamatergic activity is assumed to occur in the nucleus subthalamicus due to a decreased GABAergic input from the lateral globus pallidus. The cortico-striatal fibres also appear to be functionally over-active as the result of decreased dopaminergic nigrostriatal activity. By contrast, the glutamatergic thalamo-cortical pathway shows reduced activity due to GABAergic influence on the ventrolateral thalamus (Riederer and Berger, 1991).

The only anti-glutamatergic drugs available for the treatment of Parkinson's disease are the non-competitive NMDA receptor antagonists amantadine and memantine, which have only moderate anti-akinetic efficacy compared to dopamimetic substances (Schwab et al., 1969). However, threshold doses of memantine producing mild anti-akinetic effects result in pharmacotoxic psychosis in an unexpectedly high proportion of patients (Riederer et al., 1991). Amantadine is known to have anti-parkinsonian effects and pharmacotoxic psychoses are frequent adverse reactions (Danielczyk, 1973). In Parkinson's disease there is a lack of data

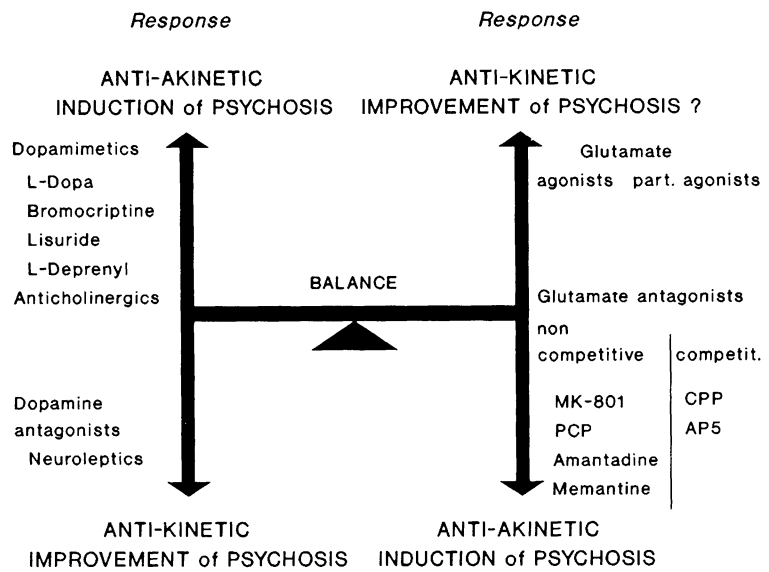

Fig. 1. Simplified illustration of glutamatergic-dopaminergic imbalances: anti-akinetic effects and psychosis

confirming a disturbance of glutamatergic function in limbic and cortical areas and supporting a glutamatergic hypothesis of pharmacotoxic psychosis. However, the fact that memantine has a considerable potential to induce pharmacotoxic psychosis at threshold doses which produce minor anti-akinetic effects, could suggest that glutamatergic activity in areas responsible for psychosis is reduced. Since under-active glutamatergic systems are further inhibited by NMDA receptor antagonists, adverse reactions such as pharmacotoxic psychosis are more likely to occur.

It is well known that all dopamimetic substances cause pharmacotoxic psychosis in Parkinson's disease and are able to aggravate productive symptoms in schizophrenia. It is not known, however, whether competitive NMDA receptor antagonists, which are known to enhance locomotor activity in experimental animals (Svensson et al., 1991; Löschmann et al., 1991), have potent anti-akinetic efficacy in Parkinson's disease or whether these substances also create the adverse reactions of dopamimetics and non-competitive NMDA receptor antagonists. The development of competitive glutamatergic antagonists or of partial agonists/antagonists could be another strategy capable of producing anti-akinetic effects with only mild side-effects. A simplified summary of this hypothesis is given in Fig. 1.

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