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Glutamate in the Mammalian CNS

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Summary. The excitatory amino acid glutamate plays an important role in the mammalian CNS. Studies conducted from 1940 to 1950 suggested that oral administration of glutamate could have a beneficial effect on normal and retardate intelligence. The neurotoxic nature of glutamate resulting in excitotoxic lesions (neuronal death) is thought possibly to underlie several neurological diseases including Huntington's disease, status epilepticus, Alzheimer's dementia and olivopontocerebellar atrophy. This neurodegenerative effect of glutamate also appears to regulate the formation, modulation and degeneration of brain cytoarchitecture during normal development and adult plasticity, by altering neuronal outgrowth and synaptogenesis. In addition to its function as a neurotransmitter in several regions of the CNS, glutamate seems to be specifically implicated in the memory process. Long-term potentiation (LTP) and long-term depression (LTD), two forms of synaptic plasticity associated with learning and memory, both involve glutamate receptors. Studies with antagonists of glutamate receptors reveal a highly selective dependency of LTP and LTD on the *N*-methyl-D-aspartate and quisqualate receptors respectively. The therapeutic value of glutamate receptor antagonists is being actively investigated. The most promising results have been obtained in epilepsy and to some extent in ischaemia and stroke. The major drawback remains the inability of antagonists to permeate the blood-brain barrier when administered systemically. Efforts should be directed towards finding antagonists that are lipid soluble and able to cross the blood-brain barrier and to find precursors that would yield the antagonist intracerebrally.

Key words: Glutamate – Intelligence – Learning – Memory – Neurological disease – Neuro-disorders

Introduction

Biochemical research revealing a central role in neural functioning for glutamic acid (Weil-Malherbe 1936) has been followed by a series of biological studies further implicating this substance in metabolic and neural processes. Glutamate is recognised to be both neuroexcitatory (Shinozaki and Konishi 1970; Johnston et al. 1974) and neurotoxic (Olney et al. 1974; Schwarcz and Coyle 1977).

Evidence supporting the transmitter status of glutamate has come primarily from electrophysiological and biochemical studies, pharmacological identification remaining a weak point. The difficulty with central synapses is in recording intracellularly in post-synaptic cells, although intracellular recording from mammalian central neurons has been done successfully (Engberg et al. 1979; Hablitz and Langmoen 1982; MacDonald and Wojtowicz 1982; Crunelli et al. 1982; Mayer and Westbrook 1984; Nistri et al. 1985; Nelson et al. 1986; Thomson 1986). The disadvantage of the iontophoretic technique, most commonly used in mammalian CNS experiments, is that concentrations of drugs at the receptors cannot be measured, allowing only limited studies on drug-receptor interaction (Shinozaki 1988). These problems have been circumvented to some extent by studying the invertebrate neuromuscular junction (NMJ) which can serve as a model for studying the mechanism of drug action in mammalian synapses (Katz 1966). Experience with the identification of gamma-aminobutyric acid (GABA) as an inhibitory transmitter first at the crayfish NMJ, then at mammalian synapses, provided the tools with which to approach the identification of glutamate as a neurotransmitter at the invertebrate NMJ (Takeuchi and Takeuchi 1964; Shinozaki and Ishida 1979a, b; Kawagoe et al. 1981, 1982, 1984).

Today glutamate satisfies, to a large extent, the four main criteria for classification as a neurotransmitter in the mammalian CNS: (1) it is presynaptically localised in specific neurons; (2) it is specifically released by physiological stimuli in concentrations high enough to elicit postsynaptic response; (3) it demonstrates identity of action with the naturally occurring transmitter, including response to antagonists and (4) mechanisms have been identified that will terminate transmitter action rapidly (for reviews see Fonnum 1981, 1984; Roberts et al. 1981; DiChiara and Gessa 1981).

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Early Studies on Glutamate

Interest in glutamate has ranged from its positive effects on animal learning to intelligence and personality in retarded, psychoneurotic and normal persons, and its suppression of abnormal EEG phenomena and control of epilepsy (for review see Vogel et al. 1966). It was later recognised that many of the early positive reports of the effects of glutamic acid on retardate intelligence were derived from methodologically weak studies. In 1960, Astin and Ross reviewing the available literature, concluded that no beneficial effect of glutamic acid upon retardate intelligence has been demonstrated. Reopening the issue in 1966, Vogel et al. reviewed the role of glutamic acid in cognitive behaviours and concluded that important differences had discriminated the positive and negative glutamic acid studies. The reports can be divided in two groups, those on retardate intelligence and those on normal intelligence.

Retardate Intelligence

Although Zimmerman and his colleagues (1950, 1959) reported that glutamic acid induced an increase in intellectual ability, Albert et al. (1946, 1951) believed that not intellectual ability but "non-intellective" components of intelligence such as concentration, attention, motivation and persistence were enhanced, leading to improved cognitive behaviour. For glutamic acid to be effective in the treatment of retardates, a suitable environment allowing acquisition of new skills was considered essential (Clapp 1949). The most successful studies with glutamate employed retarded school children in classroom situations (Levine 1949; Contini Poli 1950). An interesting aspect of earlier studies was the belief that glutamic acid but not glutamate salts were effective in treatment of retardates (Pallister and Stevens 1957; Albert et al. 1951). The report of Pond and Pond (1951) that glutamate salts increased epileptic activity while the opposite was true of the free acid is conceivably an effect of pH changes rather than the form in which glutamate was administered. Monosodium glutamate (MSG) after metabolism would increase blood pH and it is known that alkalosis lowers the seizure threshold (Siegenthaler et al. 1984).

Normal Intelligence

According to some reports, the efficacy of glutamic acid in improving cognitive capacity in normal subjects appears to be more pronounced than its effects on retardates. In a well-designed double-blind study using control groups matched for age, MSG was administered to a sample of boys under 10 years and another over 10 years of age. Although the younger group showed no difference in response, in the older group, glutamate-treated subjects showed higher scores on the Wechsler-Bellevue intelligence test. After medication was switched, the current glutamate group again scored better than controls (Milliken and Standen 1951). Data on monozygotic twins showed that subjects fed glutamic acid supplements showed performance superior to their twin counterparts, who were given another amino acid. When the test groups were switched, the glutamic-acid-fed group again showed better performance (Müller 1959). Superior performance consisted of greater resistance to fatigue and increased learning rates on simple tasks.

Other studies with children and adults have confirmed the superior intellectual performance of glutamic-acid-fed groups compared with their placebo controls (Koch 1954; Schwöbel and Tamm 1952). Positive studies have compared motivational and personality traits in treated and placebo-fed control groups. Glutamic-acid-fed groups were reported to experience "increased drive and heightened ability to utilize one's potential. Changes in self concept occur so that the person feels more competent and acts more competently" (Müller 1953a). Apart from the positive reports on the effect of glutamate, there have been negative studies on normal subjects which have reported that glutamic acid failed to influence performance in children or adults (see Mehl 1956, for review).

With respect to the effect of glutamate on retardate intelligence, the criticism of Astin and Ross (1960) dismissing these studies as poorly constructed (no control groups) does not always appear valid. True, many studies reporting the beneficial effects of glutamate are faulty and lack control groups, although some authors, such as Albert et al. (1946) and Zimmerman and Burgmeister (1950), have used the less acceptable method of subjects serving as their own controls. There have been, however, several studies employing appropriate controls; their results are divided almost equally between positive and negative effects (see Vogel et al. 1966, for review). Inherent in the nature of positive and negative results is the problem of intellectual assessment. When does a group show "superior performance" and how does one measure it? Critical evaluation of the reports on the effect of glutamate administration on normal and retardate intelligence would suggest that glutamic acid achieves its effects by positively affecting other personality characteristics which, if they are not intellectual traits in the narrow sense of the term, are certainly related to intellectual performance (Müller 1953a, 1959; Schwöbel and Tamm 1952; Mehl 1956). Alternatively, glutamate may increase the capacity to deal with simple or speed-related cognitive tasks (Müller 1955).

Glutamate as Neurotoxin and Neuroexcitator

There exists some confusion in the published literature concerning the neurotoxicity of glutamate. Neuronal degeneration induced by MSG or glutamate has been demonstrated in primates, hamsters, guinea pigs, rats and mice. Neuronal destruction in the brain after systemic administration of MSG is apparent in areas where the blood-brain barrier is leaky – the circumventricular regions (CVR) and contiguous structures (see Olney 1980, for review). After the initial report of Lucas and Newhouse (1957) that parenteral administration of MSG to neonatal rodents led to degenerative lesions in the retina, the subject of glutamate neurotoxicity was inten-

sively debated (Filer et al. 1979, for review). While the excitotoxic concept referring to an excitatory mechanism as the basis of toxic effects (Olney et al. 1974) is still controversial, there is little doubt as to the potential of glutamate as a neurotoxin. The arcuate nucleus of the mediobasal thalamus, a region contiguous with the median eminence is particularly vulnerable to the toxic effects of MSG. Nearly 90% of the perikarya in the hypothalamic arcuate nuclei are destroyed in the rat but axons of passage are unaffected (Greeley et al. 1978). Rats treated with MSG as neonates later developed metabolic and endocrinological abnormalities including obesity and skeletal stunting (Redding et al. 1971), reduced weights of pituitary gland and gonads (Bakke et al. 1978) and delayed puberty (Rodriguez Sierra et al. 1980). Dada and Blake (1985) reported that although MSG rats showed smaller anterior pituitary glands, luteneising hormone (LH) and follicle stimulating hormone (FSH) cells, the cells contained normal amounts of hormones. Intraperitoneal injection of MSG in neonatal rats resulted in a 90% loss of α-melanocyte stimulating hormone in hypothalamic and extrahypothalamic areas of the brain but no change in the pituitary (Eskay et al. 1979). Examining the nature and extent of brain lesions in mice related to the oral ingestion of monosodium glutamate, Lemkey-Johnston and Reynolds (1974) observed that in arcuate neuron damage, the first to be affected were glia and neurons close to the median eminence (within 15–20 min). The lesions were initiated superficially and radiated inward, suggesting an inflow of the noxious agent from the cerebrospinal fluid.

In vitro studies on cultured glioma cells (rat glioma C6) revealed the toxic effects of L-glutamate (the D isomer was not cytotoxic) within 12–24 h of addition. Following differentiation of C6 cells with cyclic adenosine monophosphate (AMP) or sodium butyrate, the cytotoxic effect of glutamate was lost (Kato et al. 1984).

Such in vitro studies could help elucidate the molecular mechanisms of glutamate toxicity. In another in vitro study the pathophysiology of hypoxic neuronal death was investigated. It was found that during hypoxia, the synaptic release of excitatory transmitters glutamate or aspartate led to neuronal death (Rothman 1984).

Duce et al. (1983) demonstrated in the glutamatergic neuromuscular system in locusts that when desensitisation was prevented by glutamate, activated glutamate receptors gated the influx of Ca^{2+} and Na^{+}, causing an ionic imbalance which resulted in cellular damage. The ability of glutamate analogues to cause similar damage corresponded to their pharmacological potency, i.e. L-quisqualate > L-glutamate > L-cysteine sulphinate > L-aspartate and L-kainate. The neurotoxicity of kainic acid, the best studied glutamate analogue, could operate through one of three proposed mechanisms:

1. Kainic acid is metabolised in the CNS to yield an unknown toxin responsible for neuronal degeneration.

2. Kainic acid releases large quantities of L-glutamate from nerve endings of glutamatergic neurons and/or inhibits the reuptake of transmitter glutamate (Lakshamanan and Padmanaban 1974). In either case toxicity would be indirect, due to excessive and persistent levels of glutamate in the synaptic cleft.

3. The toxic action of excitatory amino acids is due to direct action on either post-synaptic or extrasynaptic receptors. In the latter two mechanisms, neurotoxicity would result from imbalances in ion distributions following sustained depolarisation by released or administered glutamate (McGeer et al. 1978).

Intrastriatal injections of high doses of glutamate result in only limited damage to neurons in the area of infusion (McGeer and McGeer 1976; Olney and de Gubareff 1978; Schwarcz et al. 1978). One possible explanation for the inefficacy of glutamate injections into the striatum and other brain regions could be the presence of powerful local glutamate uptake mechanisms which rapidly remove glutamate from the synaptic cleft (Logan and Snyder 1971). Conversely, it seems conceivable that experimentally evoked or genetic defects in these efficient removal processes may lead to enhanced (toxic) synaptic accumulation of glutamate. Destruction of the glutamatergic cortico-striatal pathway in rats potentiated the neurotoxic action of L-glutamate. Injection of the glutamate uptake inhibitor DL-threo-3 hydroaspartate also caused neuronal degeneration, whereas if the cortico-striatal pathway had been removed prior to application, the uptake inhibitor was unable to induce striatal lesions. These results indicate that removal or blockade of uptake sites for glutamate increases the vulnerability of striatal neurons to the toxic effects of synaptically released glutamate (McBean and Roberts 1985).

The widespread distribution of glutamate and its actions upon neurons of many different central areas led to the assumption that it was a universal excitant. This view was supported by the presence of glutamate receptors in many areas of the CNS, such as the cerebral and cerebellar cortex, striatum, thalamus, reticular formation and hippocampus (see Cotman and Hamberger 1978). Additional research has shown that glutamate effects are neither indiscriminate nor universal (McLennan et al. 1968). Micro-iontophoretic studies have shown that whereas glutamate excites midbrain reticular neurons in the mesencephalic formation (Curtis and Koizumi 1961), more caudally located neurons are insensitive to its actions (DeMontigny and Lund 1980). CNS structures such as the midbrain reticular formation which are involved in the control of electrocortical activity use glutamate as the transmitter (Waller and Richter 1980). Micro-injections of glutamate into this area led to activation or desynchronisation of the electrocorticogram, whereas its topical application to the exposed cortex induced an increase in the amplitude of electrocortical activity (Bernardi 1982).

Behavioural correlates of the excitatory action of glutamate are not unknown. Sodium glutamate stereotactically injected into cerebral regions of the cat caused electroencephalographic seizures (Knaape and Wiechert 1970). MSG injected intraperitoneally into adult rats induced tonic-clonic seizures (Bhagavan et al. 1971). Convulsive disorders were induced in rats by intraperitoneal MSG, the frequency of incidence varying inversely with

the age of the animals (Beas-Zarate et al. 1985). Histological examinations indicated that seizure activity was not correlated with characteristic periventricular-arcuate area lesions as in neonates; instead it was postulated that a reversible change in the cerebrovascular permeability or plasma proteins occurred during convulsions (Nemeroff and Crisley 1975). Micro-injection of glutamate into the midbrain area induced "rage" in the freely moving cat. The midbrain site was the same where "defensive-rage" behaviour was elicited by electrical stimulation (Bandler 1982). Neonatal MSG altered two models of behavioural activity in rats; treated animals showed increased open field and decreased overnight activity (Katz 1983).

Subcutaneous injections of MSG given to postnatal rats resulted in aberrations in adult behaviour, affecting escape reaction, open field activity, avoidance learning and maze learning. Treated rats showed no behavioural deficits in the juvenile phase but manifested a definite decline at 12 and 34 months of age (Goldman and Stowe 1985).

The Excitotoxic Hypothesis of Neurodegenerative Disorders

In recent years considerable interest has been shown in the neurotoxic properties of excitatory amino acids and their possible relevance for the study of human neurodegenerative disorders (Zaczek and Coyle 1982; Schwarcz et al. 1984). The term "excitotoxin" has been used for a family of acidic amino acids which are neuroexcitants and produce a characteristic type of "axon-sparing" neuronal lesion. Intracerebral infusions of kainic acid and ibotenic acid in rats resulted in a morphological and biochemical picture which resembles that observed in the brains of Huntington's disease and epilepsy victims (Coyle et al. 1981).

It is assumed that in diseases such as Huntington's chorea (Schwarcz and Shoulson 1987), cerebral ischaemia (Rothman and Olney 1986), Alzheimer's dementia (Geddes et al. 1986; Maragos et al. 1987), stroke (Rothman 1984; Simon et al. 1984b), hypoglycaemia (Wieloch 1985) and epilepsy (Schwarcz et al. 1984), glutamate is involved in the degeneration of pyramidal neurons. Nerve cells are thought to die in response to events which are mediated by neuronal receptors for glutamate and/or other excitatory amino acids. High levels of glutamate and related excitatory amino acids including kainic acid (KA), quisqualic acid (QA) and *N*-methyl-D-aspartic acid (NMDA) can cause neurodegeneration of specific neurons, for example hippocampal pyramidal neurons (Olney and de Gubareff 1978; Coyle et al. 1981; Choi 1987).

High levels of glutamate have also been observed in the plasma of oligophrenic and Down syndrome patients (Mex et al. 1963; Sinet 1972). Increased rates of glutamate turnover were reported in brains of mouse trisomy 16, an animal model for Down syndrome (Sahai et al., to be published). Glutamate is probably involved in the neuropathology of these as well as other neurological disorders such as schizophrenia, bipolar depression, autism, ataxia and parkinsonism, reviewed elsewhere (Prusiner 1981; Walker 1983; Engelsen 1986; Greenamyre 1986).

The first clear evidence for the involvement of excitatory amino acid receptors in neurological disease came with the observation that NMDA antagonists could prevent audiogenic and chemically induced seizures in rodents (Czuczwar and Meldrum 1982). Subsequent investigations have demonstrated that NMDA receptor antagonists can suppress paroxysmal depolarisations and burst firing induced by convulsant drugs and kindling-like electrical stimulation (Slater et al. 1985) and can block convulsions in many animal models of epilepsy (Meldrum 1985). Comparable experiments indicate that the quisqualate/kainate receptor antagonist γ-D-glutamylaminomethylsulphonate (GAMS) can also reduce seizures in mice (Croucher et al. 1984), but only at doses which produce generalised depression of neural function. The reason why quisqualate/kainate receptors only mediate fast excitatory synaptic transmission while the NMDA receptor is involved in plasticity in disease can probably be found in the nature of the receptors (Fagg et al. 1986). Quisqualate and kainate receptors are ligand gated ion channels involving Na^+ and K^+, with reversal potentials near zero (Nowak et al. 1984; Mayer and Westbrook 1985; MacDermott et al. 1986). Thus they mediate fast depolarising responses and are insensitive to voltage. The NMDA receptor, on the other hand, is blocked near resting membrane potentials. It is voltage dependent, the voltage sensitivity being regulated by extracellular Mg^{2+}. Only when the Mg^{2+} blockade is released by prolonged depolarisation is the receptor activated. Therefore NMDA receptors possess the properties to mediate such specific processes as synaptic plasticity as also to effect neuronal death (Fagg et al. 1986; Foster and Fagg 1987).

The similarities between excitotoxic lesions and human neuropathologies have led to the proposal that the body produces its own excitotoxin, which under abnormal circumstances causes a neurodegenerative disease state. Likely candidates for such a role are *N*-acetylaspartyl glutamate, acetylcholine, L-asparatate, L-cysteate, L-cysteine sulfinate, L-glutamate, L-homocysteate, quinolinate, tetrahydrofolate and congeners. Of these the most promising endogenous excitotoxin appears to be quinolinic acid (Olney 1971; Coyle et al. 1981).

Any mechanisms of excitotoxic action would have to be mediated through specific membrane receptors. Despite the mechanistic differences between KA, ibotenic acid and quinolinic acid, the intracellular changes which eventually lead to nerve cell death may be common to all excitotoxins. Since the net result of excitotoxic application is an activation of neurons, it is possible that susceptible cells are simply excited to death, i.e. constant receptor stimulation depletes the cell of high-energy metabolites to the level where it can no longer maintain vital functions (Biziere and Coyle 1978). The ionic mechanism is unclear but probably involves Na^+ channels. Ca^{2+} also plays a role. Known to be a common mediator of cell death (Farber 1981), Ca^{2+} enters the cell through ion channels activated by excitatory amino acids, result-

ing in excitotoxic degeneration (Meldrum 1983; Berdichevsky et al. 1983). The NMDA receptor could play a role here, since Ca^{2+} permeates the receptors ion channel (MacDermott et al. 1986). A further possibility is the involvement of intracellular mediators of excitotoxic action like cyclic nucleotides, whose levels are affected by acidic amino acids (Foster and Roberts 1980). Although a biochemical link between endogenous excitotoxins and human neuropathologies remains elusive at present, pharmacological blockade of excitotoxicity may constitute a novel therapeutic strategy for the treatment of these diseases.

Glutamate Regulation of Brain Cytoarchitecture

A hypothesis gaining prominence in the last few years is that neurotransmitters can alter neuronal outgrowth and synaptogenesis (Kater and Mattson 1988). It has been proposed that glutamate could exert the kind of graded effects on neuronal outgrowth and survival which are consistent with a role for this neurotransmitter in regulating the formation, modulation and degeneration of brain cytoarchitecture during normal development and adult plasticity. Recent work in several systems has hinted at a role for glutamate, dopamine and acetylcholine in the alteration of neurite outgrowth (Frosch et al. 1986; Lankford et al. 1986; Mattson et al. 1987). Evidence supporting the involvement of glutamate comes from the fact that reductions in the arborisation of dendrites of the pyramidal neurons are seen in neurogenerative disorders like Alzheimer's disease and epilepsy where glutamate is implicated (Mehraien et al. 1975; Paul and Scheibel 1986). In the hippocampus, long-term potentiation (LTP; a glutamate-mediated synaptic process) is associated with alterations in the structure of dendritic spines of pyramidal neurons (Lee et al. 1980; Chang and Greenough 1984; Lynch 1986).

Although the cellular mechanisms underlying neuron outgrowth response to transmitters are poorly understood, an important role for calcium has been proposed in each case. Glutamate-induced calcium entry through ion channels is involved in the toxic action of excitatory amino acids (Berdichevsky et al. 1983; Retz and Coyle 1984); morphological changes in synapses associated with memory processes are also similarly mediated (Lynch 1986).

Mattson et al. (1988) have reported that non-toxic levels of glutamate regulated outgrowth in isolated hippocampal pyramidal neurons. The glutamate antagonist γ-D glutamyl glycine was able to prevent the negative effects of higher glutamate doses on dendritic outgrowth. The selective reduction of dendritic length suggests that glutamate excitotoxicity could be at the upper end of a scale of processes which at lower levels regulate dendritic geometry under normal conditions. The progression of dendritic outgrowth and its stabilisation is an integral part of development and there is considerable evidence that dendritic architecture undergoes significant changes throughout adult life (Beull and Coleman 1979; Purves et al. 1986). Interestingly, the spectrum of glutamate-induced changes on the neuroarchitecture of hippocampal cells seen in the study of Mattson et al. (1988) paralleled the graded neurodegenerative changes that are observed in brain pathologies such as epilepsy and Alzheimer's dementia where hippocampal pyramidal neurons are selectively vulnerable. During normal brain function, neurotransmitters such as glutamate presumably act within a finely tuned range. However, if glutamate activity were to exceed the normal range, abnormal changes in dendritic architecture and cell death would result in the manifestation of degenerative disorders with neurological consequences.

Glutamate in Learning and Memory

Glutamate is not only recognised as a neuroexcitator, a neurotoxin and a neurotransmitter, it is thought to be specifically implicated in the memory process. Van Harreveld and Fifkova (1974) postulated, on the basis of the spreading depression model, that glutamate released during neuronal activity is involved in the mechanism of memory. Glutamate causes, by an increase in sodium permeability of the plasma membrane of dendritic elements, an uptake of sodium chloride and water. The resulting decrease of the length resistance especially of dendritic spines would enhance the likelihood of discharge of the neurons when synapses situated on such spines are activated. L-Proline and L-glutamine, which antagonise glutamate action, were shown to suppress this effect.

It was suggested that patterned release of glutamate which occurred in localised areas of the brain during learning (van Harreveld 1977) produced a patterned facilitation of synaptic transmission. This impulse pattern was considered to be transcribed into a short-term memory trace which was subsequently replaced by a long-term memory trace. A hypothesis proposed by Lynch and Baudry in 1984 outlined the role of glutamate in memory as follows. Brief bursts of high-frequency activity cause a transient elevation of calcium which activates calpain, a membrane-associated neural proteinase that regulates glutamate receptor binding. The substrate of this enzyme is fodrin, a high-molecular-weight polypeptide which, being similar to spectrin, is assumed to link trans-membrane proteins and regulate the mobility of surface receptors (Ralston 1978; Marchesi 1979). Activation of calpain results in a break-up of the fodrin network on the synapse, producing structural and chemical changes in the post-synaptic region. As a result, previously occluded glutamate receptors are exposed, thereby increasing the magnitude of the post-synaptic response to the released transmitter (see Fig. 1). Repetition would steadily increase the number of receptors and cause greater influxes of calcium and ultimately structural changes. Thus, a type of practice effect seen in behavioural memory and LTP would occur. This effect may either correspond to that form of LTP which has a half-life of 3–6 days (Chang and Greenough 1984) or induce the formation of new "hot spots" for the insertion of glutamate receptors in the post-synaptic membranes which could remain for the lifespan of the synapse.

More recent work has questioned the validity of the Lynch and Baudry hypothesis. Tetanic stimulation did

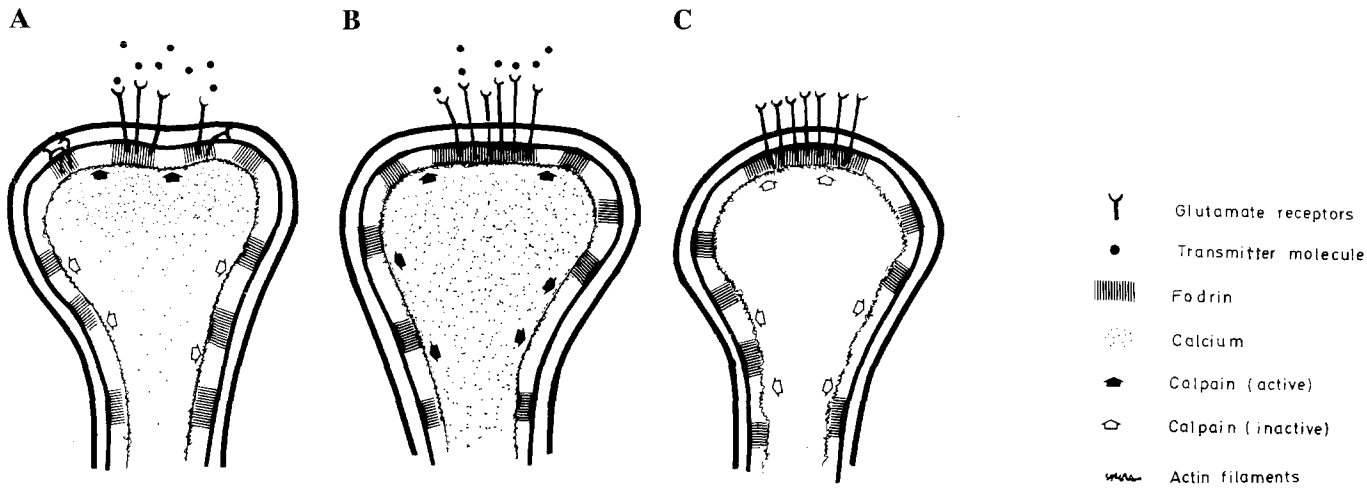

Fig. 1A–C. Calpain-mediated structural and receptor alterations resulting in long-lasting changes in synaptic efficiency. **A** Calcium-activated calpain degrades fodrin network exposing occluded glutamate receptors. **B** Subsequent synaptic activity results in greater influx of calcium due to increased number of glutamate receptors. More calpain is activated and more fodrin degraded. **C** Increased fodrin degradation allows shape changes to occur which remain even after calcium is eliminated. Adapted from Lynch and Baudry (1984)

not reproducibly increase the number of glutamate binding sites in hippocampal membranes (Lynch et al. 1985) and immunohistochemical studies have failed to provide evidence that calpain is located at synaptic sites (Hamakubo et al., in press). Moreover, Morris et al. (1987) found that leupeptin, a thiol-proteinase inhibitor, failed to modify glutamate binding to hippocampal or entrorhinal cortex membranes after a learning task in rats, although a partial impairment of spatial learning was seen. If the calpain theory were true, calpain inhibition by leupeptin should have impaired changes in synaptic efficacy, detectable as changes in glutamate binding. This was not the case. These results are also in contrast to the findings of Mamounas et al. (1984), who reported increased Cl-dependent glutamate binding in nictitating membrane conditioning in the rabbit. This discrepancy could result from the fact that only 15 spaced training trials were used in the Morris study (as against 117 in Mamounas et al. 1984) and that this amount of training was not sufficient to be detected biochemically as changes in binding.

Physiological processes in the brain that could meet the criteria of plausible intermediates of memory storage would have to be induced by brief physiological events, produce changes in the neuronal circuitry and persist for long periods. Hippocampal and cortical LTP is a stable facilitation of synaptic responses resulting from very brief trains of high-frequency stimulation (Bliss and Gardner-Medwin 1973; Bliss and Lømo 1973). Because of its persistence and modest induction conditions, LTP represents a promising candidate for a substrate of memory (Lynch and Baudry 1984; Gustafsson and Wigström 1988). The hippocampus which participates in the formation and/or retrieval of memory (Scoville and Milner 1957) and is associated with several forms of learning (see Thompson et al. 1983, for review) uses glutamate as a neurotransmitter in several of its pathways (Storm-Mathisen 1981; Storm-Mathisen et al. 1983).

Hippocampal lesions in area CA3, the neurons of which are glutamatergic (Slevin and Kasarskis 1985) cause deficits in avoidance learning (Ozaki et al. 1983). Intracortical injection of glutamate into the frontal neocortex of naive rats is reported to cause dose-related deficits in escape performance (Petty et al. 1985). The behaviour deficit was similar to shock-induced "helpless-like" behaviour but, unlike it, it could not be prevented by imipramine.

Learning and memory impairment induced by lead and zinc (Bushnell and Bowman 1979; Halas et al. 1983) are caused by inhibition of glutamate binding to hippocampal membranes (Regunathan and Sundaresan 1985; Slevin and Kasarskis 1985). Hippocampal LTP, which is induced by synaptically released glutamate (Collingridge et al. 1983), has been directly associated with an increase in the rate of learning (Berger 1984). In addition, LTP is accompanied by an increase in glutamate binding to hippocampal membranes (Baudry et al. 1980; Lynch et al. 1982; Mamounas et al. 1984). This increased binding is attributable to both activation and increase of glutamate receptors (Baudry et al. 1980; Harris et al. 1984). Calcium-dependent release of glutamate was shown to increase significantly in hippocampal CA1 region and dentate gyrus after classical conditioning in the rat (Laroche et al. 1987). This neurochemical change associated with learning is similar in nature to the increase in transmitter release seen during hippocampal LTP, and supports the hypothesis that an LTP-like mechanism is involved in learning and memory. Although work in this direction is preliminary and the results tentative, links between hippocampal LTP, on the one hand, and declarative and behavioural memory, on the other, are beginning to be established (Gustafsson and Wigström 1988; Morris et al. 1988; Barnes 1988).

Another form of synaptic plasticity associated with learning and memory is long-term depression (LTD), which ostensibly plays a role in motor learning processes

in the cerebellum. Proposed theoretically at first (Marr 1969), LTD has since been verified (Ito et al. 1982; Ito and Kano 1982; Ekerot and Kano 1985; Sakurai 1985). In the cerebellum, each Purkinje cell receives two excitatory imputs, one from a climbing fibre, the other from parallel fibres. When these two types of input are activated conjunctively, transmission between the Purkinje cell and parallel fibres undergoes LTD (Ito and Kano 1982; Ekerot and Kano 1985; Sakurai 1985). At the molecular level, LTD appears to be caused by desensitisation of glutamate receptors in the Purkinje cells. Kano and Kato (1987), on comparing glutamate receptor subtypes, found a highly selective dependency of LTD on the quisqualate receptor.

Glutamate receptors and learning

The action of glutamate is mediated by four distinct receptor systems (Watkins and Evans 1981; Davies et al. 1982; Foster and Roberts 1980; Lehmann and Scatton 1982; Luini et al. 1981; Foster and Fagg 1984; Cotman and Iversen 1987; Watkins and Olverman 1987). Three of these, the NMDA, kainate and quisqualate receptors have been defined by selective agonist actions. The fourth class is defined by the antagonist action of 2-amino-4-phosphonobutyric acid (APB). Antagonists of glutamate receptors have been shown to inhibit certain forms of learning. Glutamic acid diethyl ester (GDEE), thought to act at the quisqualate receptor, impaired instrumental learning in rats after systemic administration (Freed and Wyatt 1981). Intraperitoneally injected APB induced dose-dependent inhibition of avoidance learning in mice (Sahai et al. 1985).

However, the most promising candidate for mediating learning appears to be the NMDA receptor, which also happens to be the best studied so far. In 1986, Morris et al. reported than an NMDA receptor antagonist aminophosphonovaleric acid (AP5) not only impaired learning but also blocked LTP in the hippocampus. LTP in the hippocampus is known to be induced by glutamate activation of NMDA receptors (Kauer et al. 1988). Further support for the involvement of the NMDA receptor comes from the work of Kleinschmidt et al. (1987), who showed that AP5 disrupted experience-dependent plasticity in the striate cortex of the kitten. The anticonvulsant MK-801, which non-competitively blocks NMDA-induced responses, also blocked NMDA-receptor-mediated synaptic transmission and LTP in hippocampal slices (Coan et al. 1987). The learning process of imprinting in the chicken was associated with an almost 60% increase in NMDA-sensitive binding in the forebrain. This was attributable to an increase in NMDA receptors.

In contrast, Harris and Cotman (1986) reported that D-AP5 blocked the induction of LTP in the CA3 region of the rat hippocampus but had no effect on mossy fibre LTP. These results would suggest that LTP can be induced by at least two processes, one involving the NMDA receptor, the other independent of it. On the other hand, the results could be explained on the basis of the low density of NMDA receptors in the mossy fibre system (Cotman et al. 1987). NMDA receptors are most abundant within the telencephalon (Monaghan and Cotman 1986), the highest concentrations being found in the CA1 region of the hippocampus and the lowest in the mossy fibre termination zone (Cotman et al. 1987). LTP in the CA1 region is definitely NMDA receptor mediated (Collingridge and Bliss 1987).

NMDA receptors have been suggested to play a role in plasticity in both the developing and mature CNS. They appear to play a critical role in early learning and in the activity-dependent refinement of synaptic position during development. Ocular dominance shift, which is seen as a result of monocular visual experience, can be prevented in the kitten by NMDA receptor antagonists (Rauschecker and Hahn 1987). In the developing olfactory system, AP5 appears to block growth in focal areas of the olfactory bulb, which occurs after learning specific odours and also inhibits the neurobehavioural response to early olfactory learning (Cotman and Iversen 1987). All this would suggest that NMDA receptors play a role in the general mechanisms of developmental plasticity and learning. Learning in the mature CNS most likely involves a use-dependent strengthening of synapses. Such use-dependent strengthening mechanisms as LTP depend on NMDA receptor activation, as we have seen, and are blocked by NMDA receptor antagonists (Harris and Cotman 1986; Coan et al. 1987; Collingridge and Bliss 1987). Addressing the question of synaptic changes associated with learning, Hebb proposed, as early as 1949, a specific cellular mechanism, whereby conjunctive activity in both the pre- and post-synapse would lead to the strengthening of that synaptic connection. All subsequent models of synaptic plasticity and associative learning require mechanisms that allow change only when there is coincident pre- and post-synaptic activation (Viana Di Prisco 1984). The NMDA receptor channel allows current flow only when two conditions are met: (1) pre-synaptic activity releases transmitter that binds to the receptor; (2) the post-synaptic cell is sufficiently depolarised to relieve the voltage-dependent Mg^{2+} block of the channel. Thus the NMDA receptor complex provides the first example where Hebb-like conditions of conjunctive activity are fulfilled at a single synapse (Cotman et al. 1987).

Synaptic plasticity associated with learning could also be mediated by second messenger systems acting on excitatory amino acid receptors. Agonists at these receptors stimulate the synthesis of both cAMP and cGMP (Garthwaite 1982). More recent evidence, however, would suggest that this response is probably a general property of cerebellar tissue (Fagg et al. 1986). A more promising lead is the finding that glutamate stimulates the formation of inositol phosphates in striatal neurons (Sladeczek et al. 1985). This appears to result primarily from actions at quisqualate and NMDA receptors. Fagg and coworkers proposed in 1986 that excitatory amino acid receptor induced phosphoinositide hydrolysis would be an attractive mechanism to trigger long-term modulation of synaptic function (such as required for LTP), especially as this system may modifiy channel functions. Recently, Nicoletti et al. (1988) have provided experimental support for this hypothesis. They showed that spatial learn-

ing potentiated the stimulation of phosphoinositide hydrolysis by glutamate and ibotenate in rat hippocampus.

Therapeutic Value of Glutamate Blockers

One of the most interesting aspects to have emerged from recent research on glutamate receptors and their antagonists is the identification of compounds that could have therapeutic value. Since neurodegenerative disorders appear to result from activation of glutamate receptors (the excitotoxic hypothesis), these receptors are the logical sites for pharmacological attack. Substances with antagonist effects at these receptors could be useful as therapeutic drugs for the CNS. One drawback of many established glutamate blockers, however, is their inability to permeate the blood-brain barrier, making systematic administration ineffective.

Early glutamate blockers such as HA 966 and GDEE showed some protection against chemically induced seizures in animals but the effects were weak and variable (Bonta et al. 1969; Freed and Michaelis 1978; Abdul-Ghani et al. 1982). Later studies showed that compounds blocking excitation at the NMDA receptor are potent anticonvulsants (Croucher et al. 1982; Meldrum et al. 1983a, b). Non-selective glutamate antagonists such as cis-2, 3-piperidine dicarboxylic acid (cis 2, 3-PDA) and DGG are also anticonvulsant but, being highly polar compounds, cross the blood-brain barrier relatively poorly (Chapman et al. 1983).

One area where considerable success has been achieved with glutamate blockers is in experimental epilepsy. NMDA antagonists such as 2-amino-7 phosphonoheptanoic acid (2APH) can produce, on systemic administration, a therapeutic effect without evident neurological side-effects (Schwarcz and Meldrum 1985; Meldrum 1985). Experiments with NMDA antagonists have shown that they can suppress or prevent epileptic activity in a wide variety of seizure models (Croucher et al. 1982; Meldrum et al. 1983a, b; Avoli and Olivier 1987). 2APH and β-D-aspartylaminomethylphosphonate (ASP-AMP), when injected into cerebral ventricles of mice, are among the most potent anticonvulsants known (Jones et al. 1984; Chapman et al. 1984a, b). On systemic administration, however, 2APH has an anticonvulsant property two orders of magnitude less potent than diazepam, and more similar to valproate (Chapman et al. 1984a, b). This is because of limited entry of the antagonist into the brain (Chapman et al. 1983).

There is experimental evidence that NMDA antagonists are potential antispasticity agents. A myorelaxant effect was observed after intraperitoneal administration in the Han-Wistar rat, which has a genetically determined syndrome of spasticity (Turski et al. 1984). Antitremor effects of NMDA antagonists have been demonstrated in the high-pressure neurological syndrome (Meldrum et al. 1983c; Wardley-Smith et al. 1984). Meldrum and coworkers (Simon et al. 1984a, b; Meldrum et al. 1984) have also shown that focal injections of small amounts of 2APH into the hippocampus provide protection against the neuronal pathological changes of forebrain ischaemia and stroke. Systemic administration of MK-801 (an NMDA receptor blocker) offered protection against ischaemia-induced hippocampal neurodegeneration and epileptiform activity in rat hippocampal slices (Foster et al. 1987; Coan et al. 1987). 5-Methyl-L-Phenyl-2-(piperidinopropylamino)-hexane-1-ol (MLV-5860) is one of the most powerful glutamate blockers at the crayfish NMJ (Masaki et al. 1985; Masaki and Shinozaki 1986). This compound is capable of reducing the excessive activities of the rat nervous system (decerebrate rigidity) and reducing the frequency of spike discharges, when given intravenously (Masaki and Shinozaki 1986). A derivative of MLV-5860, MLV-6976, markedly reduced ischaemic damage in hippocampal neurons (Shinozaki 1988). A promising pharmacological role has been suggested recently for pyroglutamate, the naturally occurring cyclized internal amide of glutamic acid (Moret and Briley 1988). Pyroglutamate, which is orally active and can pass the blood-brain barrier, inhibits glutamate binding in rat striatal membranes and produces increased firing in the CA3 region of the hippocampus (Dusticier et al. 1985).

The glutamate antagonist APB, which can impair instrumental learning when administered systemically (Sahai et al. 1985), blocks synaptic transmission in the hippocampus (Ganong and Cotman 1982; Harris and Cotman 1986; Yamamoto et al. 1983; Lanthorn et al. 1984). Systemically applied APB has been shown to influence glutamate metabolism in mouse hippocampus (Nguyen and Sahai, to be published). APB also inhibited the activity of glutamate dehydrogenase and GABA-transaminase in human platelets (Miltner and Sahai, to be published) and blocked LTP in the hippocampus (Dunwiddie et al. 1978). These results would suggest that APB could play a role in areas such as memory, learning, psychosis and cognitive disorders.

Evidence is being found that the brain has endogenous neuroprotective agents to guard against glutamate damage. Kynurenic acid, a regular constituent of urine in mammals (Heidelberg et al. 1949; Musajo and Copini 1951; Brown and Price 1956; Wolf 1974) antagonises the actions of glutamate and aspartate (Perkins and Stone 1982; Robinson et al. 1984; Moroni et al. 1986) and can prevent neurodegeneration (Foster et al. 1984). Kynurenic acid has now been identified in the brains of humans and other mammals (Moroni et al. 1988; Turski et al. 1988). Moreover, it is possible to increase its concentration by administering its precursors (Moroni et al. 1988), thus providing an interesting approach to neutralise endogenous excitotoxins. The neuromodulator adenosine too is being recognised as one of the brain's natural anticonvulsants (Dragunow 1986; Burdette and Dyer 1987; Szot et al. 1987; Dragunow and Robertson 1987). NMDA-receptor-mediated cell bursting, which leads to Ca^{2+} influx into the cell and thus cell death, also leads to a massive release of adenosine (Dragunow 1986). This adenosine release, as Dragunow and Faull (1988) postulated, may reduce cell death and maintain neuronal homeostasis by a number of mechanisms. These include hyperpolarisation of neurons leading to Mg^{2+} block of NMDA receptors and also inhibiton of glutamate and acetylcholine release (Phillis and Wu 1981); inhibition of neu-

ronal Ca^{2+} uptake, block of Na^{+} uptake and compound action potentials and increased cerebral blood flow through local vasodilation and inhibition of clot formation (Ribeiro and Sebastio 1987).

The applicability of glutamate antagonists as therapeutic agents is still in its early infancy. Much work needs to be done before currently available knowledge can be transferred to the medical field. The exact effects of drugs have to be separated into components and evaluated pharmacologically. Shinozaki et al. (1987) provide an example of this approach with their work on the effects of KA and QA on drug-induced tremor in mice. Another problem that remains is the accessibility of drugs to the brain, where they are needed. Most antagonists are ineffective through the oral route or lose their effectiveness when administered systemically. The task now is to find antagonists which are lipid soluble and which can cross the blood-brain barrier or to find precursors that would yield the desired antagonist intracerebrally.

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