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The role of mammalian ionotropic receptors in synaptic plasticity: LTP, LTD and epilepsy

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Abstract. Synaptic plasticity is the foremost candidate mechanism to explain the rapid acquisition of memories. In the mammalian brain, the NMDA subclass of glutamate receptors plays a central role in the induction of several forms of use-dependent plasticity. The finding that modifications in synaptic strength are largely expressed by receptors of the AMPA subclass has focused attention on molecular mechanisms that affect their function and targeting. Receptor plasticity has also been reported in pathological situations, notably in animal and human forms of epilepsy. Which of these changes are causally implicated in the generation of seizures, and which may be compensatory or neuroprotective adaptations, has not been fully resolved.

Key words. AMPA; NMDA; kainate; GABA; receptor subunits; phosphorylation; silent synapses; status epilepticus.

Introduction

In addition to mediating rapid intercellular communication, ionotropic receptors are an important site of plasticity in the central nervous system (CNS). Changes in the properties, location and number of receptors can alter the transmission of information through neuronal circuits. This modifiability has the potential to store memories, but may also contribute to the hyperexcitability that underlies the initiation and propagation of seizures. In this review we will summarise some of the evidence that implicates ionotropic glutamate receptors in the induction and expression of two forms of mammalian experience-dependent synaptic plasticity, namely long-term potentiation (LTP) and long-term depression (LTD). We will also review some of the alterations that have been reported in GABA and glutamate receptor function in the brains of epileptic patients and experimental animals. We will not consider in detail short-lasting forms of activity-dependent synaptic plasticity that are thought to be mediated mainly by presynaptic changes in transmitter release. Nor will we discuss in detail the mechanisms by which intracellular second messengers can interact with receptors, because this subject is covered elsewhere in this issue.

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Use-dependent synaptic plasticity

LTP

LTP has attracted intense attention, not only because of its potential role as the cellular substrate for several forms of learning, but also because its underlying mechanisms have proved difficult to dissect [1, 2]. We will focus our attention on the role of ionotropic glutamate receptors in its induction and early expression.

LTP has been studied most intensively in the rodent hippocampus and neocortex, although closely related phenomena have also been reported in many other parts of the CNS. Several distinct subtypes have been identified. One is sensitive to NMDA receptor blockade, and is widely observed at synapses formed at dendritic spines on pyramidal neurons. Another form is seen at some synapses that express Ca^{2+}-permeable AMPA receptors. Finally, hippocampal mossy fibre LTP is independent of NMDA receptor activation, and

is seen principally at synapses formed on CA3 pyramidal neurons.

NMDA receptor-dependent LTP

NMDA receptor-dependent LTP can be triggered experimentally either by delivering high-frequency tetani to a critical number of presynaptic afferent fibres, or by pairing postsynaptic depolarisation with presynaptic stimulation [3]. The common feature of these induction methods is the coincidence of postsynaptic depolarisation and presynaptic glutamate release, which allows Ca^{2+} influx through NMDA receptors. LTP can be elicited even when glutamate receptors of the AMPA sub-type are blocked, as long as Ca^{2+} can enter via NMDA receptors [4, 5]. Under several experimental conditions Ca^{2+} influx via voltage-dependent Ca^{2+} channels [6–8] (or even Ca^{2+} release from photolysable caged Ca^{2+} compounds [9]) can substitute for NMDA receptor activation. Whether these alternative sources of Ca^{2+} actually contribute to LTP under more conventional recording conditions, or even in vivo, is unresolved. Indeed, it has been suggested that Ca^{2+} influx by-passing NMDA receptors may actually trigger different expression mechanisms [10].

The events downstream of NMDA receptor activation include activation of several protein kinases, of which Ca^{2+}-calmodulin kinase II (CaMKII) has attracted the greatest attention [11]. Blocking [12, 13] or knockout of CaMKII [14] prevents LTP. Conversely, introducing activated CaMKII into the postsynaptic neuron increases synaptic strength [15, 16]. These and other observations support the notion that activation of CaMKII is necessary to potentiate synaptic transmission. Other kinases may play a modulatory role in LTP, by phosphorylating a number of target proteins, including NMDA receptors [17]. A fuller discussion of the involvement of this and other molecules in LTP is given in [18].

The final targets of the intracellular biochemical cascade are the subject of a major controversy. The main options are: (i) an increase in the average probability that a presynaptic glutamate vesicle is released from the presynaptic terminal following action potential invasion; (ii) an increase in the amount of glutamate contained in a presynaptic vesicle; (iii) a change in the spatial and/or temporal concentration profile of glutamate so that receptors are exposed to a higher peak concentration; (iv) a change in the properties of postsynaptic glutamate receptors, so that their response to glutamate is enhanced; (v) an increase in the number of receptors present and (vi) an increase in the number of synapses.

It is likely that different phenomena underlie LTP expression at different times following its induction. We will concentrate on the involvement of ionotropic receptors in the changes that occur in the first hour or so, during which time protein translation is not necessary [1].

A major experimental obstacle is that LTP is generally only induced at a small fraction of synapses, making it difficult to interpret measurements of glutamate concentrations in the extracellular space, or of the postsynaptic sensitivity to exogenous glutamate receptor agonists [1]. Instead, the most compelling insights into LTP expression mechanisms have come from examining changes in signals elicited by activity in the same axons as were stimulated during the induction.

An important argument against a simple presynaptic increase in transmitter release probability is that LTP is not associated with a large change in short-term activity-dependent facilitation [19–22] (although see [23, 24]). This observation stands in contrast to the effects of pharmacological manipulations that alter transmitter release probability, which almost uniformly alter short-term facilitation [21]. Arguing in favour of a postsynaptic change in glutamate receptors is that LTP is associated with a relatively greater increase in the size of the signal mediated by AMPA receptors than that mediated by NMDA receptors [4, 5, 25, 26] (although see [27]). This implies that AMPA receptors may undergo a relatively selective alteration in their properties, or in the number of receptors available to detect presynaptic glutamate release. In the context of these observations, an unexpected finding was that quantal analysis generally reveals an increase not only in the average quantal amplitude mediated by AMPA receptors [28], but also in the mean number of quanta (quantal content) [29–33]. The increase in quantal content is actually most simply explained by a presynaptic increase in transmitter release probability. Much experimental effort has been directed at resolving this paradox. An important breakthrough was made by discovering that under baseline conditions, there is a marked discrepancy between the quantal content mediated by AMPA and NMDA receptors [26, 37, 38]. At CA1 synapses in the rodent hippocampus, NMDA receptors appear to detect roughly twice as many quanta of glutamate than do AMPA receptors. Because LTP is largely mediated by an increase in quantal content mediated by AMPA receptors, this observation led to the so-called silent synapse hypothesis. According to this model, AMPA receptors are initially absent or nonfunctional at a population of synapses, but can be recruited by the induction of LTP.

Before considering the anatomical evidence that AMPA receptors are absent at some synapses, it is important to draw attention to an alternative interpretation of the discrepancy between AMPA and NMDA receptor-mediated signalling. AMPA receptors have a much lower

affinity for glutamate than do NMDA receptors [39]. This implies that a synaptic signal purely mediated by NMDA receptors could be generated even if both receptors were present within the postsynaptic density, on condition that the glutamate concentration was insufficient to open the AMPA receptors. There are two ways in which this could happen [40]. First, insufficient glutamate could enter the synaptic cleft from the presynaptic terminal. And second, a vesicle of glutamate could be released fully, but at a neighbouring synapse rather than at the synapse of interest. If this neighbouring synapse were located sufficiently close by, then 'spillover' of glutamate could again give rise to a signal purely mediated by NMDA receptors. Evidence for heterosynaptic interactions mediated by glutamate diffusion is accumulating [40–46]. Intersynaptic spillover has profound implications for the interpretation of the relatively selective increase in AMPA receptor-mediated signals during LTP [40].

The spillover hypothesis and the postsynaptically silent synapse hypothesis are not mutually exclusive, and a major challenge is to determine their relative importance. Recently, immunohistological methods have been applied to determining whether there is a population of synapses devoid of AMPA receptors, where they could be recruited in a quantal manner. Several groups have applied the postembedding immunogold technique to estimate the distribution of AMPA and NMDA receptors at hippocampal synapses [47–50]. This presents major challenges to optimise the sensitivity of the method, and to recognise receptors composed of different subtypes, many of which undergo posttranscriptional and posttranslational modifications. Nevertheless, a proportion of small synapses appears to be devoid of AMPA receptors, whereas NMDA receptors are more uniformly distributed. The proportion of AMPA-devoid synapses has been estimated as between 9 and 14% in adult rodents. Although this is less than the proportion of silent synapses suggested by electrophysiological approaches (approximately 50%), glutamate spillover may account for the discrepancy.

What alterations of AMPA receptor function could underlie the postsynaptic expression of LTP? Quantal analysis reveals an increase in both quantal amplitude and quantal content [31–36].

The increase in quantal amplitude could be mediated by a quantitative alteration in the function of individual receptors, such that the opening probability and/or the single channel conductance increased. Of these alternatives, the latter is more attractive because LTP is not associated with a change in the time-course of the synaptic response [51]. How might the single channel conductance be increased? LTP-inducing stimuli have been shown to lead to an increased proportion of phosphorylated AMPA receptors [52]. GluR1 (GluRA) subunits can, moreover, be phosphorylated by CaMKII [and by protein kinase C (PKC)] at a serine residue at position 831 [53, 54]. Interestingly, other AMPA receptor subunits do not have corresponding consensus sites for these kinases. Ser831 phosphorylation has been shown to lead to an increased open channel conductance in recombinant receptors [55], providing a possible mechanism for the increase in quantal amplitude seen in LTP. Supporting this hypothesis, an increase in single channel conductance has also been reported for native AMPA receptors in situ, following LTP induction [56].

Although the scheme outlined above provides an attractive link from CaMKII activation to synaptic potentiation, it is not such a good candidate for the increase in quantal content. In order to explain this observation, an entire cluster of AMPA receptors would have to become available at a synapse where they are initially absent. Attention has recently focused on the possibility that AMPA receptors could be translocated into the postsynaptic density from a dendritic store [57]. In support of this hypothesis, molecules that interfere with vesicle exocytosis, when injected into postsynaptic neurons, block the induction of LTP [58]. Furthermore, optical imaging of receptors tagged with green fluorescent protein (GFP) has shown an alteration in their distribution following stimuli that induce LTP [59]. Although this suggests that these receptors may be rapidly translocated into dendritic spines, the interpretation of the data is confounded by the formation of new spinelike processes over a similar time scale [60, 61]. Moreover, there is no convincing evidence that a vesicular store of receptors exists within the postsynaptic dendrite, so the hypothesis that clusters of receptors can be rapidly delivered to the postsynaptic density remains unproven.

In contrast to the increase in quantal amplitude, which may require phosphorylation of GluR1, it has recently been suggested that the translocation of clusters of AMPA receptors depends on interactions between GluR2 (GluRB) and the ATPase *N*-ethylmaleimide sensitive factor (NSF), which is important for membrane fusion events [62–64].

In the light of the potentially complementary roles played by GluR1 subunits (mediating a graded increase in channel current) and GluR2 subunits (mediating receptor translocation), it is interesting to examine the alterations in LTP induction and expression in animals with genetic deletion of one or other subunit. GluR2 knockout mice show greater than normal LTP induced by tetanic stimulation, part of which is resistant to blockade of NMDA receptors [65]. This may be explained by the fact that GluR2 subunits normally confer Ca^{2+} impermeability to AMPA receptors [66]. GluR2-deficient receptors may offer an additional route

for Ca^{2+} entry into the postsynaptic spine under conditions of intense presynaptic glutamate release. Because GluR2 receptors cannot act as the downstream target of the Ca^{2+}-triggered cascade in these animals, LTP must be expressed by another mechanism, for instance phosphorylation of GluR1 subunits. In animals deficient in GluR1, in contrast, tetanic LTP is absent in the CA1 region of the hippocampus, although it persists at a reduced level in the dentate gyrus [67]. It is unclear whether this reflects a deficit in induction of LTP, which might be overcome by pairing presynaptic stimulation with postsynaptic depolarisation, or failure to express LTP, for instance because a critical target substrate for CaMKII (namely GluR1) is absent (Fig. 1).

Figure 1 summarises the salient features of the role of inotropic receptors in LTP.

Synaptic plasticity triggered by Ca^{2+}-permeable AMPA receptors

The finding that LTP is enhanced in animals deficient in GluR2 is especially interesting because this subunit is often absent at some synapses on nonpyramidal neurons in wild-type animals. This observation prompts the suggestion that a form of use-dependent LTP might be observed even in the presence of NMDA receptor blockers. Such a phenomenon has, indeed, been reported at synapses in the amygdala [68] and dorsal horn [69]. An interesting aspect of LTP triggered by Ca^{2+}-permeable AMPA receptors is that Ca^{2+} influx is likely to be maximal when presynaptic glutamate release coincides with postsynaptic hyperpolarisation. This is because GluR2-deficient receptors characteristically show an inwardly rectifying current-voltage relationship. At a network level, plasticity may thus be expected to follow different rules, with regard to the coincidence of pre- and postsynaptic activity, than NMDA receptor-dependent LTP. Although synapses with Ca^{2+}-permeable AMPA receptors are also seen in hippocampal interneurons, tetanic stimulation induces long-term depression (see below) rather than LTP [70]. This observation implies that additional factors determine the sign of the change in synaptic strength.

Mossy fibre LTP

Another form of LTP that does not require a coincidence of pre- and postsynaptic activity is seen at hippocampal mossy fibre synapses on CA3 pyramidal neurons. Broad spectrum ionotropic glutamate receptor

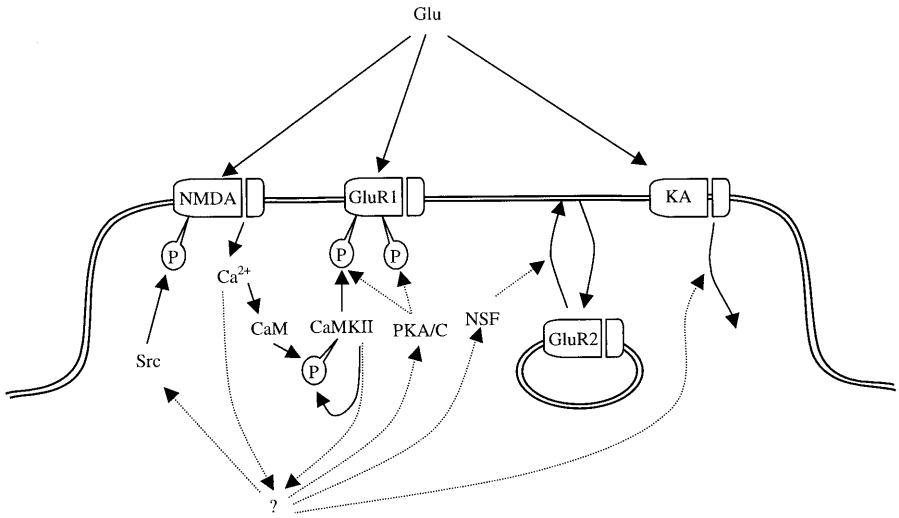

Figure 1. Ionotropic receptors in NMDA receptor-dependent LTP. The continuous arrows show the signalling pathways for which most evidence exists: Ca^{2+} influx via NMDA receptors triggers the phosphorylation of CaMKII (which can be sustained by autophosphorylation), and CaMKII, in turn, phosphorylates GluR1 AMPA receptor subunits. The broken arrows show signalling pathways for which the evidence is less secure. Protein kinases A and C (PKA/C) can phosphorylate GluR1 subunits, although whether this takes place in LTP is unclear. NMDA receptors can be modulated by the tyrosine kinase Src, a possible example of 'metaplasticity' that regulates the induction of LTP. AMPA receptor-mediated signals appear at synapses where they were previously silent. One potential mechanism is a modulation of NSF/GluR2-mediated incorporation of AMPA receptors into the postsynaptic density. Some evidence exists that impairment of a constitutive NSF/GluR2 interaction may occur in LTD, but as yet there is no convincing evidence that this interaction is enhanced in LTP. Finally, kainate receptor-mediated signals have been reported to decrease following LTP induction in early life. The question mark indicates uncertainty over the identities of the biochemical triggers for these phenomena.

blockers, reversibly applied before tetanic stimulation, fail to prevent its induction [71], implying that AMPA, kainate and NMDA receptors play no role in the phenomenon. The recent report that a selective antagonist of the GluR5 subtype of kainate receptors prevents mossy fibre LTP induction [72] thus comes as a surprise. The expression of mossy fibre LTP appears to be presynaptic. A simple (although not universally held—see [73]) view of LTP in this system is that high-frequency firing of presynaptic afferent fibres triggers a rise in cyclic AMP (cAMP) in presynaptic terminals, which leads to a persistent enhancement of transmitter release probability [71].

Synapse development

A process akin to NMDA receptor-dependent LTP may underlie the maturation of synapses in young animals. Immunogold labelling of synaptic receptors at different ages shows that the proportion of synapses apparently devoid of AMPA receptor gradually falls with age [47, 50]. In the first postnatal week, synaptic responses mediated exclusively by NMDA receptors are gradually replaced by dual-component (AMPA and NMDA receptor-mediated) synapses, and this conversion can be rapidly induced by pairing presynaptic stimulation with postsynaptic depolarisation [74]. Although this observation makes a suggestive link between development and learning, the subcellular mechanisms are again incompletely understood. Synaptic responses purely mediated by NMDA receptors could reflect glutamate spillover from neighbouring terminals [40] in addition to the absence of functional AMPA receptors. Notably, glutamate transporters are expressed at very low levels in the first few days of life [75], potentially allowing the transmitter to diffuse extensively following exocytosis.

Another unresolved issue is how postsynaptic depolarisation, apparently required for the induction of synapse maturation, could occur in vivo in the absence of functional AMPA receptors. An attractive suggestion is that $GABA_A$ receptor-mediated responses are depolarising in very young animals [76]. The coincidence of presynaptic glutamate release with postsynaptic $GABA_A$ receptor-mediated depolarisation could then determine which synapses undergo the maturation event.

Although attention has focused on the induction of an AMPA receptor-mediated component at previously silent synapses, this may not be the only change that takes place during synapse maturation. A very small and slow kainate receptor-mediated synaptic signal has been reported in cortical neurons, which is gradually replaced by a fast AMPA receptor-mediated component [77]. Pairing presynaptic stimulation with postsynaptic stimulation appears to induce an analogous but rapid switch. The slow kinetics of the kainate receptor-mediated component are poorly understood, because native and recombinant kainate receptors in isolated cells show a low affinity for glutamate and rapid kinetics, akin to those of AMPA receptors [78].

LTD

LTD refers to a persistent decrease in synaptic strength triggered by specific activity patterns. At several synapses in the hippocampus of immature animals prolonged trains of low-frequency stimulation are followed by a decrease in the size of the synaptic signal [79]. At least two forms of LTD can also be separated pharmacologically. One phenomenon depends on Ca^{2+} influx via NMDA receptors, and requires the action of protein phosphatases [80, 81]. This finding has lent support to the view that an LTD-LTP continuum exists, and that the sign and size of the change in synaptic strength is determined by the amplitude of the Ca^{2+} influx [82, 83]: a brief but large Ca^{2+} surge tips the balance towards phosphorylation of downstream targets, and leads to LTP, whereas a more prolonged but modest Ca^{2+} increase leads to dephosphorylation and LTD. A second form of LTD requires metabotropic receptor activation for its induction. This has been described at CA1 [84] and dentate gyrus [85] synapses, and at mossy fibre synapses on CA3 pyramidal neurons [86].

An unusual form of LTD has been described at synapses on hippocampal interneurons equipped with Ca^{2+}-permeable AMPA receptors: a persistent depression in transmission is triggered by a high-frequency tetanus, and requires both postsynaptic Ca^{2+} influx and activation of presynaptic metabotropic receptors [70].

Decreases in both the average quantal amplitude and the average quantal content underlie the expression of LTD [87]. Although this might imply that LTD is simply the reverse of LTP, some subtle but important differences have been pointed out. For instance, a chemical treatment that may mimic LTD causes dephosphorylation of GluR1 at residue ser845, which is a target of protein kinase A (PKA) [88], rather than at ser831, which is phosphorylated by CaMKII. Moreover, it has been reported that NMDA receptor-dependent LTD is accompanied by a decrease in quantal amplitude, whereas metabotropic receptor-dependent LTD is expressed by a decrease in quantal content [89]. Resolving the synaptic locus of the decrease in quantal content presents the same challenges as for the opposite change seen in LTP.

A further form of LTD is seen at parallel fibre-Purkinje cell synapses, where it is widely thought to subserve cerebellar learning [90–93]. Briefly, LTD occurs when a parallel fibre synapse discharges at the same time as the climbing fibre supplying the Purkinje cell [93]. A necessary event for the induction of LTD is a local Ca^{2+}

surge, but there is some disagreement whether this is sufficient. The climbing fibre-induced depolarisation elicits a moderate and diffuse Ca^{2+} influx via voltage-sensitive Ca^{2+} channels. Glutamate release from the parallel fibre synapse contributes further local depolarisation as well as Ca^{2+} release from intracellular stores mediated by metabotropic receptors [94–96]. This local Ca^{2+} signal, on its own [97] or together with nitric oxide [98–100] and/or Na^{+} influx [101], then leads to a modification of AMPA receptors, rendering these less sensitive to glutamate. The molecular mechanism of this modification is poorly understood. Protein kinases C and G (PKC and PKG) are involved in the intracellular cascade [102–104]. PKG is especially interesting because its substrate, in the phosphorylated state, is a powerful inhibitor of phosphatases, possibly resulting in a local molecular switch. However, this leads to a paradox: phosphorylation of GluR1 receptors, as suggested to occur in hippocampal LTP, results in an increased conductance. How phosphorylation, possibly at a different site, could result in decreased channel function in Purkinje cells, has not been determined.

Plasticity of ligand-gated channels in epilepsy

The plasticity that is necessary for normal CNS development and function can potentially underlie epilepsy. Neuronal death, neurogenesis, synaptic reorganisation and changes in receptor expression have all been implicated in the epileptogenesis. The interpretation of many of the experimental findings, however, is confounded by the difficulty in differentiating effects that play a causal role in epileptogenicity from compensatory changes, and from the results of seizures or antiepileptic drug treatment. Many experimental studies that have reported alterations in ionotropic receptors in human epilepsy have relied on neuroimaging (using positron emission tomography with radioligands such as the benzodiazepine antagonist flumazenil), and histopathology (using immunohistochemistry, autoradiography and in situ hybridisation). The changes that are observed in human or animal studies must be controlled for changes in the density of neurons and synapses. It is often difficult to differentiate excitatory from inhibitory neuronal populations and thus to determine which signalling pathways are affected. Moreover, many human studies fail to define accurately the underlying aetiology of the epilepsy, and also suffer from technical difficulties such as time from resection or postmortem to histological analysis. It is thus not surprising that these studies arrive at conflicting results [105]. We will concentrate on changes in ionotropic receptors in the hippocampus because relatively few adequately controlled studies have looked at extratemporal epilepsy, and because hippocampal sclerosis is a major cause of drug-resistant epilepsy.

Glutamate receptors and synaptic plasticity in epilepsy

Many useful insights into the aetiology of limbic/hippocampal epilepsy have come from the rodent kindling model [106]. The kindling phenomenon shares several characteristics with NMDA-dependent LTP of excitatory synaptic transmission [107, 108]. These similarities have been taken to suggest that kindling and LTP are very similar in respect to underlying mechanisms. In support of this, the rate at which kindling occurs is retarded in rodents treated with NMDA receptor antagonists. However, these drugs do not completely block kindling at doses that completely block the induction of LTP. Furthermore, while the kindling process requires afterdischarges, LTP induction without afterdischarges does not induce kindling. Thus, LTP of glutamatergic synaptic transmission may contribute to kindling by increasing the excitatory synaptic drive and the likelihood of evoking afterdischarges, but is alone insufficient to explain the cellular mechanisms of kindling [107, 108].

Both synaptic and nonsynaptic factors probably contribute to the hyperexcitability seen in the kindled hippocampus. One synaptic phenomenon that has attracted considerable attention is an alteration in the function of NMDA-receptor mediated synaptic responses [109]. Several studies indicate that NMDA receptor subunit mRNAs undergo differential regulation during kindling [110–112]. Kindling also results in fast and long-lasting posttranslational modifications in the function of NMDA receptor channels, leading to increases in the mean open time, burst and cluster duration, and to decreases in the channel blocking effect by magnesium [113]. Similar changes in NMDA channels have recently been reported in human epileptic tissue [114]. The modification of the NMDA receptor channels may result from a decrease in the activity of intracellular phosphatases, leading to an increased phosporylation of the receptors [115]. These changes could play an important role in lowering the threshold for the initiation and spread of seizures.

In comparison with NMDA receptors, there is relatively little evidence that AMPA receptors are modified by kindling. Prolonged seizures themselves, however, may lead to alterations in the expression of AMPA and kainate receptor subunits [116–118]. In sclerosed human hippocampi from patients with temporal lobe epilepsy, there is an upregulation of GluR2/3 immunoreactivity in the dentate granule cells and hilus [119]. An increase in the expression of the Ca^{2+}-impermeable AMPA receptor subunit GluR2 in dentate granule cells could have a neuroprotective role, and could

help explain the relative resistance of kindled rats to kainic acid-induced neurotoxicity [120]. Alternatively, it could represent a selection process, so that neurons expressing fewer Ca^{2+}-permeable AMPAs are relatively resistant to seizure-induced neuronal death.

As discussed earlier, there is evidence that glutamate can escape from the synaptic cleft to activate extrasynaptic receptors, or even receptors at neighbouring synapses [40]. This 'spillover' model of glutamatergic signalling differs from the view that glutamate 'leakage' only occurs in the presence of major metabolic perturbations which prevent or even reverse active glutamate uptake by membrane pumps [121]. Extrasynaptic accumulation of glutamate may play a role in epilepsy: rodents lacking the gene coding for the glial glutamate transporter GLT-1 (EAAT2) show lethal spontaneous seizures [122]. Rather surprisingly, chronic administration of antisense oligonucleotides to knock down the same transporter produces a different phenotype, characterised by neurodegeneration rather than seizures [123]. Reduction of expression of the neuronal transporter EAAC1 (EAAT3), however, also causes seizures in rats. Subtle alterations in transporter levels have been reported in hippocampal tissue taken from patients with temporal lobe epilepsy [124], although it is again difficult to determine to what extent this reflects selective neurodegeneration.

Extrasynaptic glutamate diffusion might affect not only postsynaptic ionotropic receptors at neighbouring excitatory synapses but also presynaptic receptors at inhibitory synaptic terminals [125]. Activation of presynaptic kainate receptors can reduce both GABAergic [126, 127] and glutamatergic transmission [128] in the CA1 region of the hippocampus. These results have been taken to suggest that disinhibition may play a role in triggering seizures. In support of this, synaptically released glutamate can also reduce GABAergic signalling in vitro [129].

The GluR3 subtype of glutamate receptors has recently been implicated in the pathogenesis of Rasmussen's encephalitis, a rare disorder characterised by progressive focal epilepsy. Autoantibodies to GluR3 are present in a proportion of patients, some of whom respond to immunomodulation [130].

$GABA_A$ receptors in epilepsy

Pharmacological reduction in GABA-mediated inhibition in the central nervous system is a powerful proconvulsant stimulus. There are, however, conflicting data in animal models of epilepsy as to whether there is up- or downregulation of GABA-mediated inhibition [131]. The general finding is that acute, prolonged seizures can result in a breakdown of inhibition, whereas upregulation seems to occur in chronic models of epilepsy. The acute changes have been suggested to be the result of 'disconnection' of inhibitory interneurons—the so-called dormant basket cell hypothesis [132–134]. Receptor changes also seem to occur during acute seizures. It has been noted that as seizures continue they become less responsive to benzodiazepines, and this is mirrored by a decreased potency of benzodiazepines on GABA-mediated synaptic currents in dentate granule cells [135]. In contrast, the potency of GABA itself and pentobarbitone remained unaltered, suggesting that rapid changes in GABA receptor properties occur during seizures.

In general in chronic epileptic models, there is an upregulation of inhibition. This is associated with increases in the number of receptors per synapse [136], as well as increases in the number of synapses [137]. Recently, increased presynaptic release of GABA has been reported following febrile convulsions in rodents [138]. An especially interesting finding is that the increased GABA receptor-mediated signalling to dentate granule cells becomes more sensitive to zinc [139]. In order to understand the potential involvement of zinc in epilepsy, it is necessary to consider the role of mossy fibres, which normally project from granule cells to CA3. During the epileptogenic process, these fibres sprout collaterals that feed back into the dentate granule cell layer, setting up local excitatory circuits [140, 141]. This sprouting, however, not only increases excitation but also contributes to the synaptic drive onto inhibitory interneurons, so inhibition is upregulated. Thus mossy fibres form excitatory circuits that are normally suppressed, but which can result in epileptiform activity when synaptic inhibition is blocked [142]. Mossy fibre terminals contain zinc, and release it during synaptic activity. Thus, it is conceivable that in the epileptic hippocampus, zinc released from mossy fibres results in disinhibition, unmasking the potentiated excitation and so resulting in seizures. A decreased sensitivity of $GABA_A$ receptor-mediated signals to zolpidem (a selective benzodiazepine agonist) has also been noted [143]. This change, together with the increased sensitivity to zinc, has been ascribed to a change in the relative expression of α_1, α_4 and β subunits. Notably, the changes were seen in the latent period that predated the occurrence of epilepsy, supporting a role in epileptogenesis.

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