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Review

The use of the hippocampal slice preparation in the study of Alzheimer's disease

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Abstract

In the present article we show how studying synaptic mechanisms in hippocampal slice preparations provides information that may be useful in, firstly, the understanding of the aetiology of Alzheimer's disease and, secondly, in the development of novel therapies for dementia. We use several examples, drawn from our own work: (i) The identification of the function of AMPA receptors and NMDA receptors in synaptic transmission and synaptic plasticity. (ii) The discovery of mechanisms that can regulate the activation of NMDA receptors. (iii) The use of transgenic models of Alzheimer's disease. (iv) The identification of a mechanism that can account for the cognitive enhancing effects of the NMDA receptor antagonist memantine. (v) The discovery of a role of glycogen synthase kinase-3β (tau kinase) in synaptic plasticity.

Keywords: Synaptic plasticity; Hippocampus; Alzheimer's disease; Memantine; Glycogen synthase kinase-3β; Glutamate

Contents

1. The role of glutamate receptors in hippocampal synaptic transmission and synaptic plasticity

In the early 1980s it was assumed that *S*-glutamate was the principal excitatory neurotransmitter at synapses in the hippocampus but the involvement of specific glutamate receptor subtypes was unknown. However, the development of selective NMDA receptor antagonists (Watkins and Evans, 1981), enabled the role of this subtype to be determined. The first studies were performed using the Schaffer collateral-commissural pathway, which connects CA3 and CA1 pyramidal neurons (CA3–CA1 synapses). It was found that NMDA receptors were not involved, to any appreciable extent, in the response to single stimuli evoked by low frequency stimulation, but their activation was required for the induction of long-term potentiation (Fig. 1A; Collingridge et al., 1983; see Bliss and Collingridge, 1993 and Bliss et al., 2007 for detailed reviews of long-term potentiation). The principle that NMDA receptors are the trigger for long-term potentiation has since been extended to

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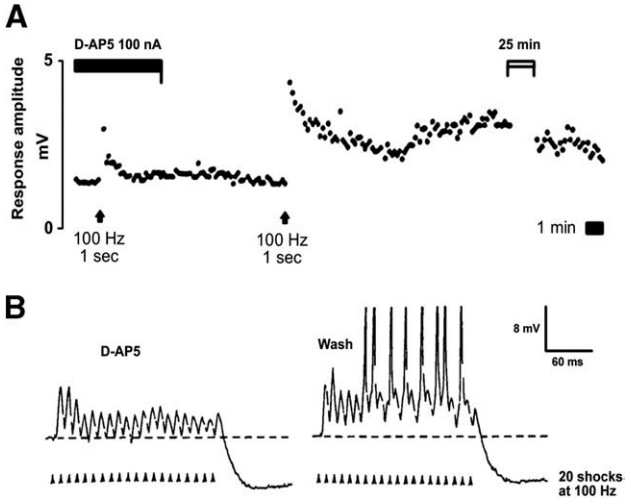


Fig. 1. NMDARs trigger the induction of long-term potentiation and mediate a component of the synaptic response during high frequency transmission. (A) A plot of synaptic response amplitude vs time. A tetanus delivered in the presence of D-AP5 induced only post-tetanic potentiation (PTP), whereas an identical tetanus delivered in the absence of D-AP5 induced long-term potentiation. Data re-plotted from Collingridge et al.,1983. (B) Synaptic potentials in response to 20 shocks delivered at 100Hz in the presence and following washout of D-AP5. In the absence of D-AP5 there is an additional slow depolarisation, which in this neuron summated with the fast AMPAR-mediated EPSPs to induce action potential firing. Data from Herron et al., 1986.

many other synapses in the brain. Subsequently, it was also found that NMDA receptors are triggers for the induction of depotentiation (Fujii et al., 1991) and long-term depression of basal transmission (Dudek and Bear, 1992). Thus, NMDA receptors are triggers of synaptic plasticity but do not determine the direction of the change in synaptic efficacy.

The reason that NMDA receptors contribute minimally to low frequency transmission is due to the Mg^{2+} block (Ault et al., 1980; Nowak et al., 1984), which is intensified by the hyperpolarising influence of concurrently activated GABAergic synaptic inhibition (Herron et al., 1985; Dingledine et al., 1986). During high frequency transmission there is a depolarisation of the postsynaptic neuron which temporarily alleviates the Mg^{2+} block and thereby enabling NMDA receptors to contribute to the synaptic response (Ault et al., 1980; Collingridge et al., 1988). The requirement for presynaptic activity to provide *S*-glutamate and postsynaptic activity to provide the depolarisation to alleviate the Mg^{2+} block endows NMDA receptor-dependent synaptic plasticity with "hebbian" properties (Bliss and Collingridge, 1993). We shall refer, therefore, to the depolarisation that is required to remove the Mg^{2+} block as "hebbian depolarisation".

NMDA receptors are mainly permeable to Na^{+} and K^{+} and so their activation leads to additional depolarisation. This depolarisation can be sufficient to enable a neuron that does not fire action potentials for a given input to then do so (Fig. 1B; Herron et al., 1986)—in other words, NMDA receptors can contribute greatly to the synaptic output. Given that high frequency burst discharges constitute a common form of neural activity, this means that NMDA receptors are major contributors to synaptic transmission, as well as being the primary trigger for synaptic plasticity in the brain. Amongst other things, this has major implications for the numerous investigations that have tried to infer the function of NMDA receptor-dependent synaptic plasticity in behaviour, using pharmacological or genetic approaches. In addition to being permeable to monovalent cations, NMDA receptors are also permeable to Ca^{2+} (MacDermott et al., 1986). Entry of Ca^{2+} via synaptically-activated NMDA receptors (Alford et al., 1993) is believed to confer input specificity, such that only synapses that receive sufficient activation of NMDA receptors will undergo plasticity.

The development of antagonists also enabled the identity of the receptor that mediates low frequency synaptic transmission to be identified. The first compound used, γ-D-glutamylglycine suggested that it was an AMPA or kainate type receptor (Fig. 2A; Collingridge et al., 1983). The subsequent development of more selective antagonists, such as the quinoxalinediones 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) and 2,3-dioxo-6-nitro-1,2,3,4-tetrahydrobenzo[f]quinoxaline -7-sulfonamide (NBQX; Honore et al., 1988) and the 2,3-benzodiazepines (e.g. GYKI53655), showed that it was the AMPA receptor that mediates this response (Fig. 2B; Blake et al., 1988; Davies and Collingridge, 1989). The induction of long-term potentiation was not associated with any change in sensitivity to CNQX (Fig. 2C), showing that potentiation involved a modification of the efficiency of AMPA receptor-mediated synaptic transmission, rather than the recruitment of a different type of receptor (Davies et al., 1989). Therefore, most studies that wish to understand how

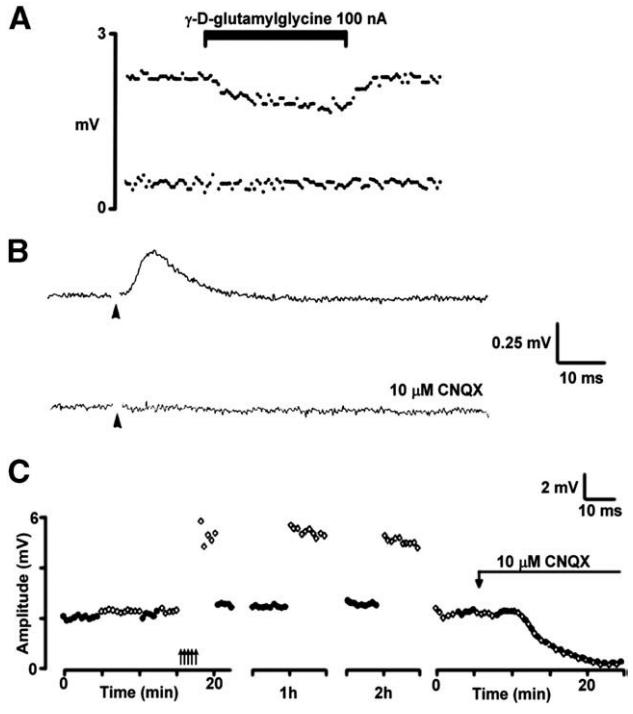


Fig. 2. AMPARs mediate the modifiable fast synaptic response. (A) The weak AMPAR antagonist γ-D-glutamylglycine depresses fast synaptic transmission at CA3–CA1 synapses. From Collingridge et al., 1983. (B) The potent AMPA receptor antagonist CNQX blocks fast synaptic transmission at CA3–CA1 synapses. From Blake et al., 1988. (C) Potentiated and non-potentiated inputs have identical sensitivity to CNQX. From Davies et al., 1989.

synaptic plasticity is expressed have focussed on the properties and cell biology of the AMPA receptor (Collingridge et al., 2004). It should be noted, however, that the NMDA receptor can also mediate a modifiable synaptic response (e.g. Bashir et al., 1991).

So how is the hebbian depolarisation produced during the induction of long-term potentiation? A primary factor is the temporal summation of AMPA receptor-mediated EPSPs (Bliss and Collingridge, 1993). In addition, as NMDA receptors become activated they contribute to the hebbian depolarisation, providing a positive feedback effect. There may also be alterations in ionic activities, such as an increase in extracellular K^+. A major regulator is GABAergic inhibition (Davies et al., 1991). This ordinarily inhibits the synaptic activation of NMDA receptors by enhancing the Mg^{2+} block. If EPSPs and IPSPs simply summated during high frequency transmission then the inhibition would continue to prevent the synaptic activation of NMDA receptors. Instead, what happens is that there are acute plastic changes in GABAergic inhibition. Synaptic inhibition is transiently reduced to enable the synaptic activation of NMDA receptors, an effect mediated by the synaptic activation of $GABA_B$ autoreceptors. This mechanism is particularly effective at the theta frequency, since feedback inhibition of GABA release is maximal at around 5–10Hz. On the other-hand, this mechanism is negated by longer-lasting trains, such as occurs during the commonly used "tetanus" (Davies and Collingridge, 1996). This is because there is a depolarising shift in the $GABA_A$ reversal potential, and indeed under these conditions $GABA_A$ receptors may actually contribute to the hebbian depolarisation rather than oppose it.

This mechanism has implications for understanding the regulation of long-term potentiation. For example, $GABA_B$ antagonists completely prevent the induction of long-term potentiation when theta patterns are used but not when tetanus is employed or $GABA_A$ inhibition is blocked (Davies and Collingridge, 1996). In otherwords, $GABA_B$ receptors are powerful regulators of synaptic plasticity, that may have an important role during the induction of long-term potentiation under physiological conditions, but their role can be bypassed and easily missed. The same is likely to be true of other regulators of synaptic plasticity. The mechanism of induction of NMDA receptor-dependent long-term potentiation is shown schematically in Fig. 3.

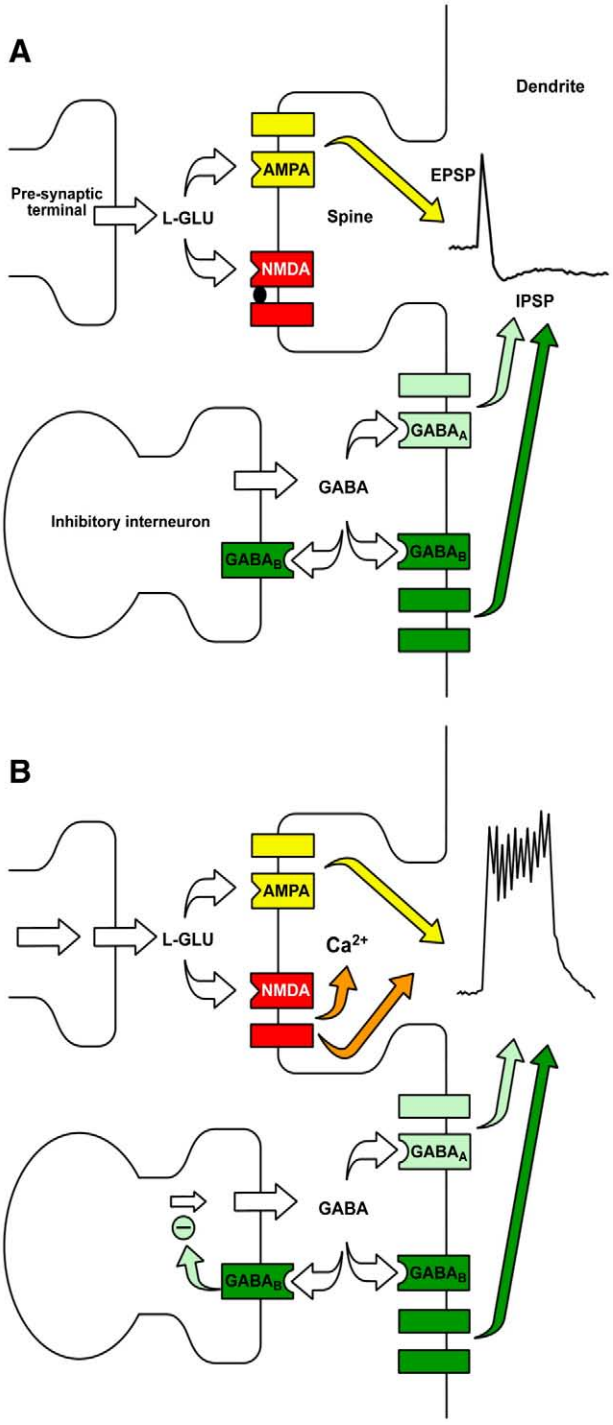
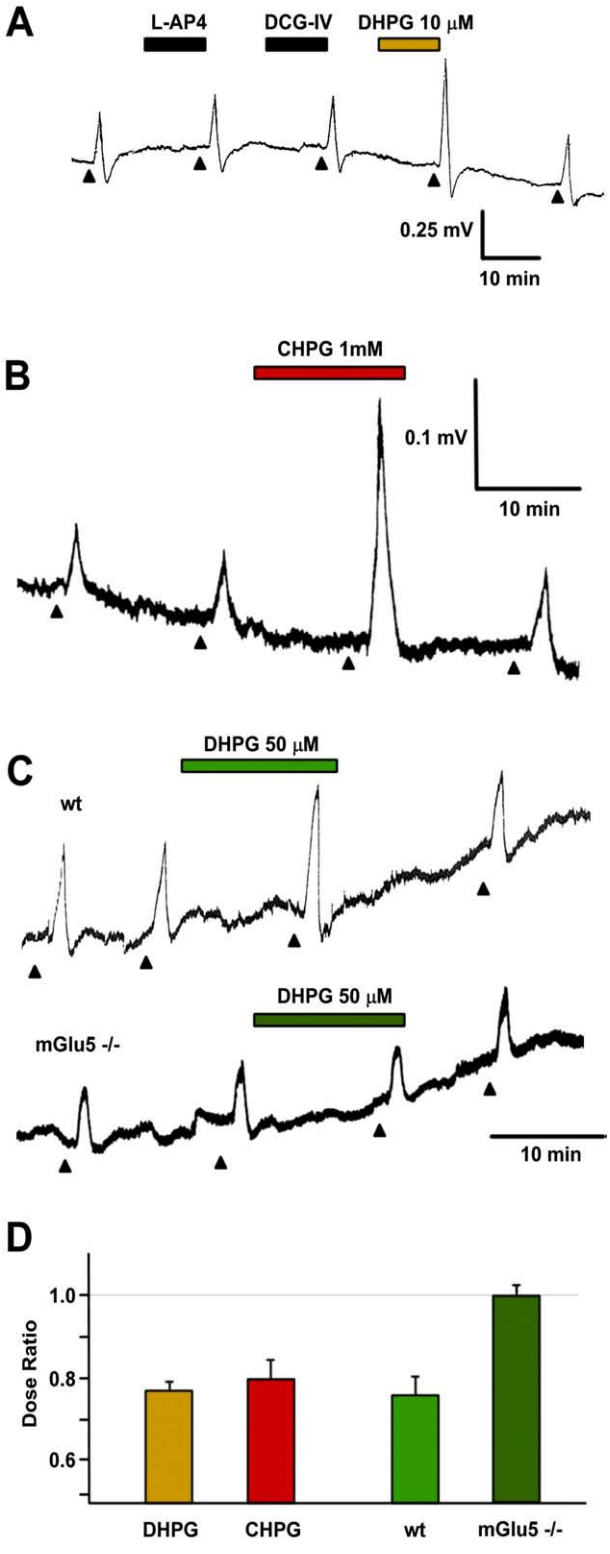


Fig. 3. A scheme that summarises the induction of long-term potentiation. (A) Shows an EPSP–IPSP sequence mediated by the synaptic activation of AMPARs, GABAA and GABAB receptors. There is essentially no activation of the NMDA receptor because Mg^{2+} blocks the channel. (B) During high frequency transmission the extra depolarisation (hebbian depolarisation) repels the Mg^{2+} from the channel whilst the receptors are activated by *S*-glutamate. This hebbian depolarisation is due to the summation of AMPA receptor- and NMDA receptor-mediated EPSPs. The reduction in synaptic inhibition, caused by the feedback of GABA onto presynaptic $GABA_B$ autoreceptors is important to enable the hebbian depolarisation during theta-type patterns of activation. Modified from Bliss and Collingridge, 1993.

2. Regulation of NMDA receptors

Since the NMDA receptor is the principal trigger for the induction of long-term potentiation at many synapses in the brain there has been considerable interest is identifying ways of facilitating its activation. This could be useful in conditions where there may be a hypo-function of NMDA receptor-mediated synaptic plasticity, such as potentially in schizophrenia and dementia. One such mechanism is to activate group I mGlu receptors. Examples of the potentiation of NMDA responses by activation of mGlu5 receptors (Fitzjohn et al., 1996; Doherty et al., 1997) is illustrated in Fig. 4. Of course, such a regulation would not only affect long-term potentiation but could also affect

long-term depression, depotentiation and high frequency synaptic transmission. The most effective regulation would be via allosteric potentiation, so that the compound only acted at synapses whilst they were undergoing synaptic activation. Such a strategy has already been employed (Chen et al., 2007).



3. Hippocampal synaptic mechanisms in transgenic models of Alzheimer's disease

Alzheimer's disease is a neurodegenerative disease first characterised by the physician Alois Alzheimer in 1907, who described an elderly female patient with severe cognitive impairment and characteristic post-mortem brain pathology. Alzheimer's disease is the most prevalent form of dementia, constituting around 50% of dementia cases worldwide and affecting between 24% and 33% of people aged over 85 in the Western world (Blennow et al., 2006).

The amyloid hypothesis is the dominant current hypothesis for how Alzheimer's disease is caused (Blennow et al., 2006; Hardy and Selkoe, 2002; Newman et al., 2007). The extracellular plaques seen in brains of Alzheimer's disease patients are composed of deposited non-soluble amyloid β-protein, a product of the cleavage of amyloid precursor protein. Amyloid precursor protein is a cell membrane protein that is cleaved by a variety of enzymes to yield products of varying length. Cleavage by α secretase enzymes produces short length fragments which are non-amyloidogenic. However, sequential cleavage by β and γ secretases produces amyloid β-protein of either short (amyloid β-protein 40) or long (amyloid β-protein 42) form; the length being determined by the precise cleavage site of the γ secretase. Amyloid β-protein 42 is much less soluble and therefore gives rise to plaque deposition. Much research has shown that mutations in amyloid precursor protein along with presenilin 1 and presenilin 2 (two proteins contributing to γ secretase activity) contribute the majority of familial cases of Alzheimer's disease, although such cases only account for less than 10% of total Alzheimer's disease cases (Blennow et al., 2006). The precise series of events leading to dementia is still a matter of speculation, but involves an immune response, altered neuronal homeostasis, altered kinase and phosphatase activity, synapse loss and cell death. In particular the production of intracellular tangles of hyperphosphorylated tau protein are a key part of Alzheimer's disease, as the presence of these tangles are correlated with the progression of dementia, whereas amyloid β-protein plaques may be present before the onset of dementia.

The hippocampus is one of the brain regions affected during the early stages of Alzheimer's disease, and this, along with the memory deficits associated with Alzheimer's disease, naturally led to the hypothesis that hippocampal synaptic transmission and plasticity may be impaired in animal models of Alzheimer's disease (Seabrook and Rosahl, 1999). To this end hippocampal function in vitro has been investigated in several transgenic

Fig. 4. Facilitation of NMDA responses by the activation of group I mGlu receptors. (A) shows depolarisations of CA1 neurons induced by brief prefusion with NMDA (25μM) at times denoted by triangles. Co-application of the group I mGlu receptor agonist DHPG, but not the group II or III agonists DCG-IV or L-AP4, potentiated the NMDA response in a reversible manner. Data from Fitzjohn et al., 1996. (B) The mGlu5 receptor selective agonist CHPG potentiates NMDA responses. From Doherty et al., 1997. (C) DHPG potentiates NMDA responses in wildtype but not mGlu5$^{-/-}$ mice. Data from unpublished experiments of R. Schnabel and G. Collingridge. (D) Quantification of the results. The graphs plot potentiation expressed as dose–ratio (1.0 equals no effect) for the pooled data of the experiments shown in panels A–C.

mouse strains carrying mutations in Alzheimer's disease-related proteins such as amyloid precursor protein and presenilin 1. A full review of all of this work is outside the scope of this review, so we shall mainly concentrate on work that we have been involved in to demonstrate the nature of these studies.

Our initial work utilised an amyloid precursor protein knockout mouse to elucidate whether amyloid precursor protein itself had a role in hippocampal synaptic plasticity (Fitzjohn et al., 2000; Seabrook et al., 1999). The amyloid precursor protein knockout mice showed normal basal synaptic transmission in area CA1 of the hippocampus, but long-term potentiation was found to be significantly reduced in knockout mice compared to wildtype littermate controls at both 1 and 2years of age (Seabrook et al., 1999). Although the basic biophysical properties of pyramidal neurones in the amyloid precursor protein knockout mouse were similar to wildtypes, neurones showed a decrease in overall size and in the depth of their projection into the stratum radiatum of CA1, suggesting a possible role for amyloid precursor protein in normal neuronal development. Subsequently, it was shown that although long-term potentiation was impaired in amyloid precursor protein knockout mice when induced by a theta burst stimulus (Fig. 5Ai), this deficit was lost when long-term potentiation was induced using a strong tetanus under conditions where $GABA_A$ receptor-mediated transmission was inhibited (Fig. 5Aii; Fitzjohn et al., 2000). Thus the deficit in long-term potentiation seen in amyloid precursor protein knockout animals does not appear to be due to an impairment in long-term potentiation expression mechanisms, but may be a consequence of other changes in the hippocampus. Indeed, preliminary data suggests that their may be alterations in GABA-mediated inhibition, that indirectly affects the induction of long-term potentiation (Fitzjohn et al., 2000).

Similar to studies on mice lacking amyloid precursor protein, work on mice underexpressing presenilin 1 show normal synaptic transmission but reduced long-term potentiation (Fig. 5B; Morton et al., 2002)). These mice express only one copy of the presenilin 1 gene, as deletion of all presenilin 1 results in embryonic death due to disruption of somite development (Shen et al., 1997).

Although use of an amyloid precursor protein knockout mouse may provide insights into the normal function of amyloid precursor protein and its metabolites such as amyloid β-protein, they are not useful as a model of Alzheimer's disease as the amyloid β-protein plaques seen in Alzheimer's disease brains are lacking. Thus more useful studies have been performed with mice expressing mutated forms of Alzheimer's disease that are related to familial forms of Alzheimer's disease in humans. Examples of these are the Swedish, Flemish and Dutch amyloid precursor protein mutations, all of which result in an altered amyloid β-protein 40/42 ratio such that the amyloid β-protein 42 proportion is increased (Newman et al., 2007). Transgenic mice overexpressing the Swedish mutant variant of amyloid precursor protein (APP_{SWE}) is a commonly studied mouse line. Here the 695 amino acid amyloid precursor protein protein carries the double point mutation K670N and M671L (Hsiao et al., 1996).

Experiments on hippocampal synaptic transmission and plasticity using APP_{SWE} transgenic mice revealed an impairment of basal excitatory synaptic transmission that appears to be, at least in part, due to an increased risk of excitotoxic damage during in vitro slice preparation in APP_{SWE} mice compared to wildtype littermate control animals (Fitzjohn et al., 2001). In animals of 12months of age, basal responses were depressed in APP_{SWE} mice compared to controls, but this deficit was not seen when hippocampal slices were prepared in media containing a broad spectrum glutamate receptor antagonist (kynurenic acid), which will act to limit neuronal damage caused by excessive activation of ionotropic glutamate receptors during periods of inevitable hypoxia during the slicing procedure. However, slices from 18month old animals, which contain enhanced levels of amyloid β-protein compared to 12month old animals, showed a deficit in basal synaptic transmission which is not prevented by using kynurenic acid during slice preparation (Fig. 5Ci; Fitzjohn et al., 2001). Interestingly, even at 18months of age when basal synaptic transmission is impaired, long-term potentiation appears normal in APP_{SWE} mice (Fig. 5Cii). A later study replicated these observations in a different transgenic line but with the same mutation, showing reduced basal glutamatergic transmission but normal long-term potentiation in APP_{SWE} mice (Fig. 5D; Brown et al., 2005), along with normal GABAergic transmission. This latter study also found changes in synchronous network activity, which is likely to alter hippocampal function.

Studies into synaptic hippocampal transmission and plasticity using amyloid precursor protein transgenic mice have produced inconsistent results. For example, another study on the APP_{SWE} mouse found normal basal transmission but reduced long-term potentiation (Chapman et al., 1999). The reason for this discrepancy is not known but could, perhaps, relate to differences in the housing conditions or prior experience of the animals. Mice with the Indiana mutation in amyloid precursor protein (V717F) show reduced basal transmission with normal long-term potentiation (Hsia et al., 1999), whereas the mice with the London mutation (V642I) show reduced long-term potentiation (Moechars et al., 1999). What can be concluded from these studies is that long-term potentiation can be elicited normally which means that the long-term potentiation process per se is not a primary deficit in these mouse models. However, long-term potentiation may under certain circumstances be reduced. This might be a secondary consequence of, for example, the reduction in synaptic transmission affecting the ability to reach the co-operativity threshold for long-term potentiation.

A disadvantage of the amyloid precursor protein and presenilin 1 mutations as transgenic models of Alzheimer's disease is that the pathology seen in these mice does not mimic the disease state in humans, in particular they do not exhibit intracellular tangles of hyperphosphorylated tau, despite the presence of amyloid β-protein plaques (Ashe, 2005). More recent use of mice expressing multiple mutated proteins linked to Alzheimer's disease may provide a better model of the disease. For example, mice expressing mutated presenilin 1, amyloid precursor protein and tau (mutations presenilin 1: M146V; APP_{SWE}; tau P301L) show progressive development of amyloid β-protein plaques and tau tangles over their lifespan,

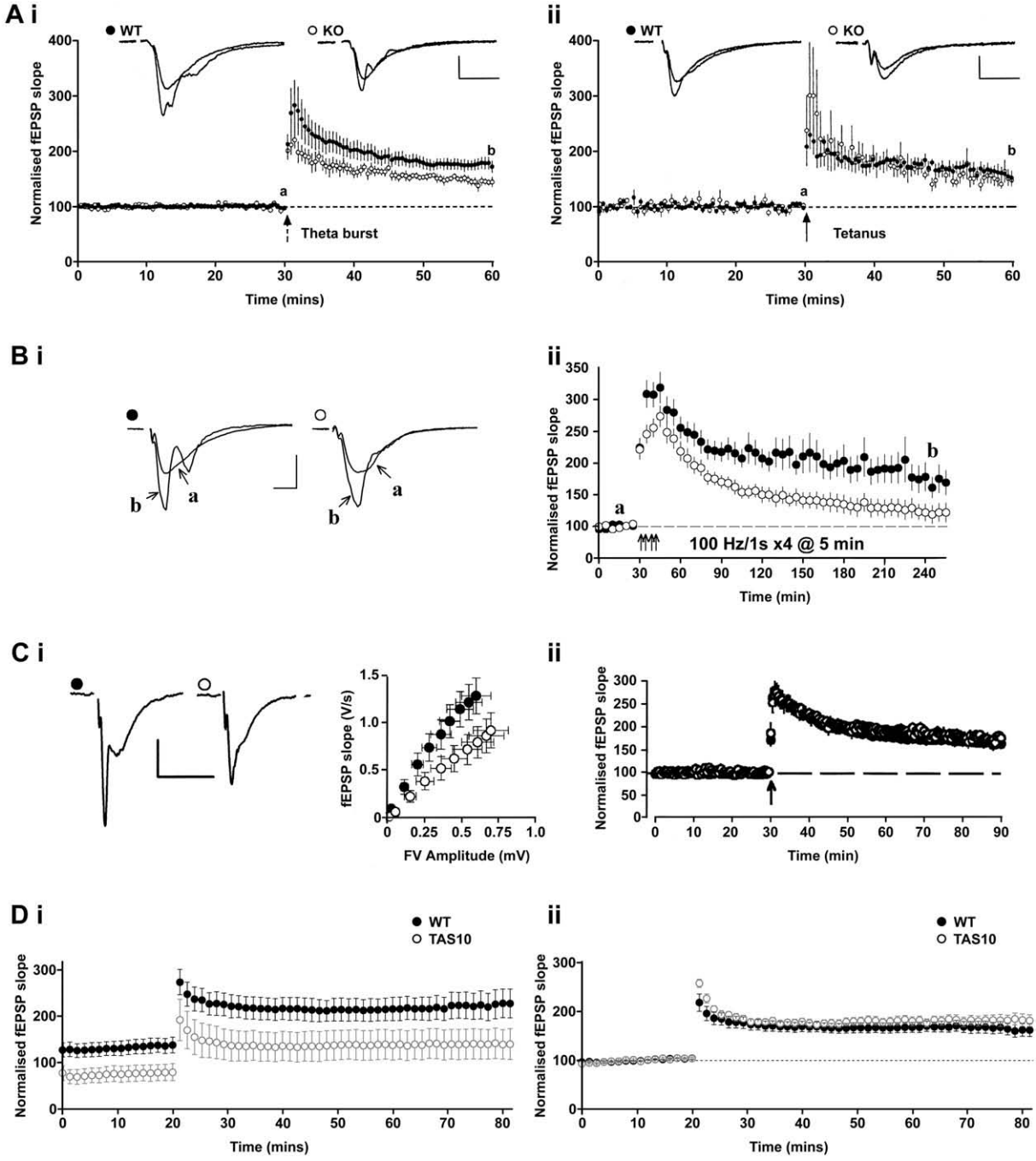


Fig. 5. Alterations in synaptic transmission and long-term potentiation in transgenic models of Alzheimer's disease. (Ai). In the amyloid precursor protein knockout mouse, long-term potentiation induced by a theta burst stimulus is reduced compared to wildtype littermate controls. (Aii) This deficit in long-term potentiation is not seen when a strong tetanus is used to induce long-term potentiation in the presence of the $GABA_A$ receptor antagonist picrotoxin. Data in panels A and B adapted from Fitzjohn et al., 2000. (B) Presenilin 1 heterozygote knockout animals show normal synaptic transmission but reduced long-term potentiation compared to wildtype animals. Panel Bi shows example traces before (a) and after (b) long-term potentiation for wildtype (filled circles) and presenilin $1^{+/-}$ animals (open circles), Bii shows long-term potentiation induced by a strong tetanus protocol. Data adapted from Morton et al., 2002. (Ci) In the APP_{SWE} mouse basal synaptic is impaired. Input–output curves plotting presynaptic fibre volley (FV) amplitude versus fEPSP slope show a reduction in the transgenic (open circle) compared to wildtype (filled circle) animals, (Cii) Despite the reduction in basal synaptic transmission, long-term potentiation induced in the APP_{SWE} transgenic mouse is identical to the wildtype controls. Data adapted from Fitzjohn et al., 2001. (D) In a separate study, the APP_{SWE} mouse (also named TAS10) was also found to have reduced basal transmission but normal long-term potentiation. In panels Di experiments are plotted normalised to basal response across both groups, showing reduced basal transmission in the TAS10 mice. (Dii) experiments are normalised to the baseline for each group, showing normal long-term potentiation in the TAS10 mice. Data adapted from Brown et al., 2005.

and also exhibit a marked reduction in hippocampal long-term potentiation (Oddo et al., 2003). Such studies may provide further insight into the synaptic dysfunctions produced during the development of Alzheimer's disease.

4. Memantine can facilitate synaptic plasticity

Given that NMDA receptors are involved in the induction of long-term potentiation, and other forms of synaptic plasticity, it may seem counter-intuitive that an NMDA receptor antagonist, such as memantine, demonstrates efficacy in the treatment of Alzheimer's disease (Danysz and Parsons, 2003). This compound has been introduced into the clinic for the treatment of moderate to severe Alzheimer's disease where it seems to both improve cognition and slow the progression of the disease.

A clue to how an NMDA receptor antagonist might improve cognition is shown in Fig. 6. In experiments to establish the role of the Mg^{2+} block of NMDA receptors in long-term potentiation we attempted to induce long-term potentiation after slices had been perfused with a Mg^{2+}-free ACSF, a treatment that greatly enhances the synaptic activation of NMDA receptors (Coan et al., 1989). To our initial surprise we found that this treatment completely prevented the induction of long-term potentiation by tetanus (Fig. 6A). This was not because the perfusion with Mg^{2+}-free medium had resulted in the induction and saturation of long-term potentiation, since long-term potentiation could be

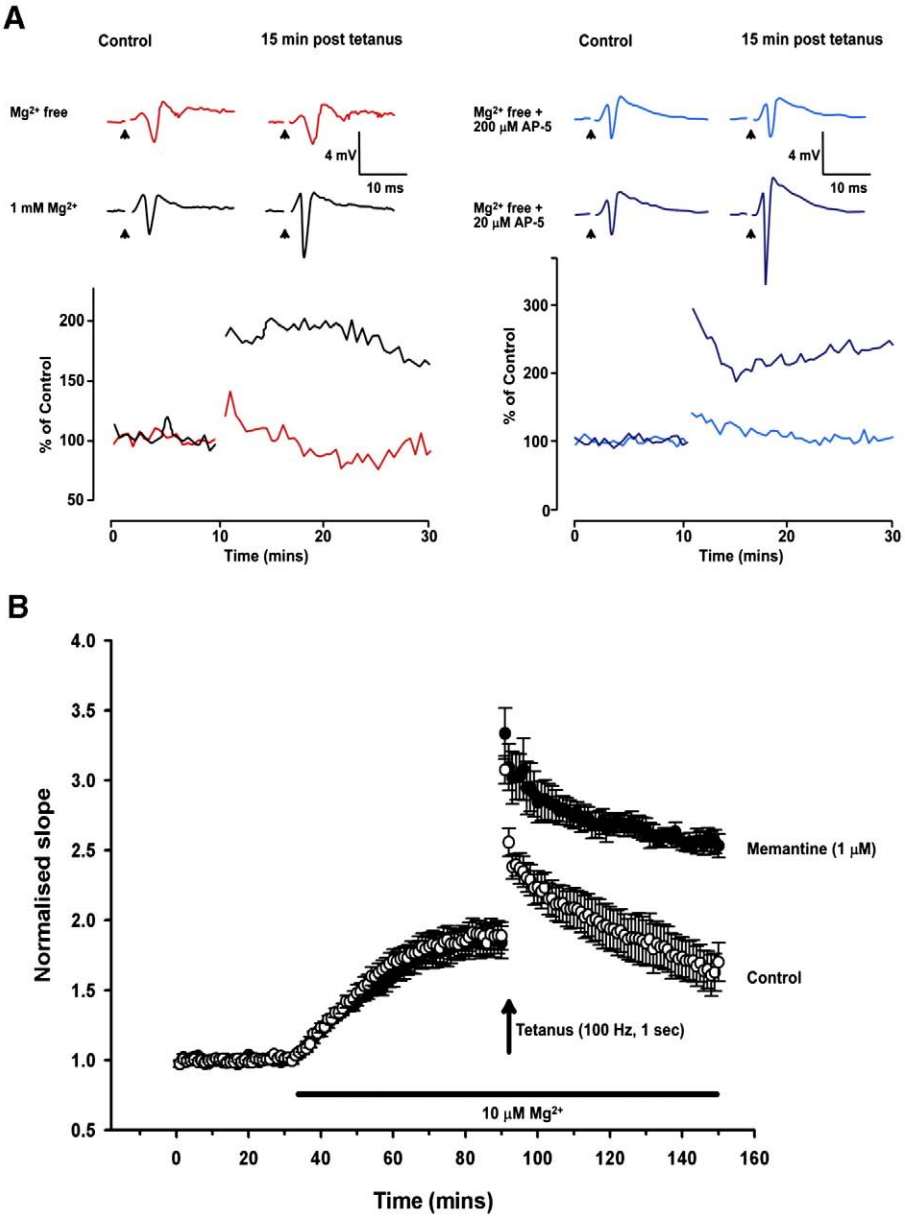


Fig. 6. Inhibiting NMDA receptors can facilitate NMDA receptor-dependent long-term potentiation. (A) Long-term potentiation is absent in slices perfused with Mg^{2+}-free media, but can be obtained when Mg^{2+} is re-introduced. long-term potentiation can, however, be obtained in Mg^{2+}-free medium when a low, but not a high, concentration of D-AP5 is applied. Re-plotted from Coan et al., 1989. (B) A low, but not a high, concentration of memantine also enables the induction of long-term potentiation in Mg^{2+}-free media. Modified from Frankiewicz and Parsons, 1999.

readily induced following the addition of Mg^{2+} to the perfusate. Rather it was due to the inappropriate activation of NMDA receptors before and/or after the tetanus, since long-term potentiation could be induced when an NMDA receptor antagonist was added to the Mg^{2+}-free perfusate. The NMDA receptor antagonist, in this case D-2-amino-5-phosphonopentanoate, was added at a concentration (20μM) that suppressed the synaptic activation of NMDA receptors during low frequency stimulation but not during the tetanus (because the greater amount of *S*-glutamate could overcome the competitive block). If the concentration of D-AP5 was increased 10-fold then long-term potentiation was blocked, showing that the long-term potentiation was of the NMDA receptor-dependent variety. Thus, long-term potentiation requires NMDA receptor activation to be minimised at times other than when long-term potentiation is to be induced. This situation is somewhat analogous to an action potential; an action potential is triggered by a brief strong depolarisation whereas a sustained weak depolarisation results in inactivation of the action potential.

Memantine works in a similar manner. Thus, a low dose of memantine (1μM) enables long-term potentiation to be induced in Mg^{2+}-free conditions (Frankiewicz and Parsons, 1999), whereas a high dose (10μM) blocks the induction of long-term potentiation in normal conditions (Fig. 6B; Frankiewicz et al., 1996). In this case memantine blocks the NMDA receptor in a voltage-dependent manner, but the principle is similar. Of course, cognitive deficits in Alzheimer's disease are unlikely to be due to a reduction in extracellular Mg^{2+}. However, it is very plausible that neurons become depolarised, for example due to a reduction in the energy available to maintain the resting membrane potential. Under these conditions the Mg^{2+} block will be reduced and NMDAR activation will occur at inappropriate times. Memantine could, at least partially, compensate for the reduced Mg^{2+} block thereby enabling long-term potentiation-like

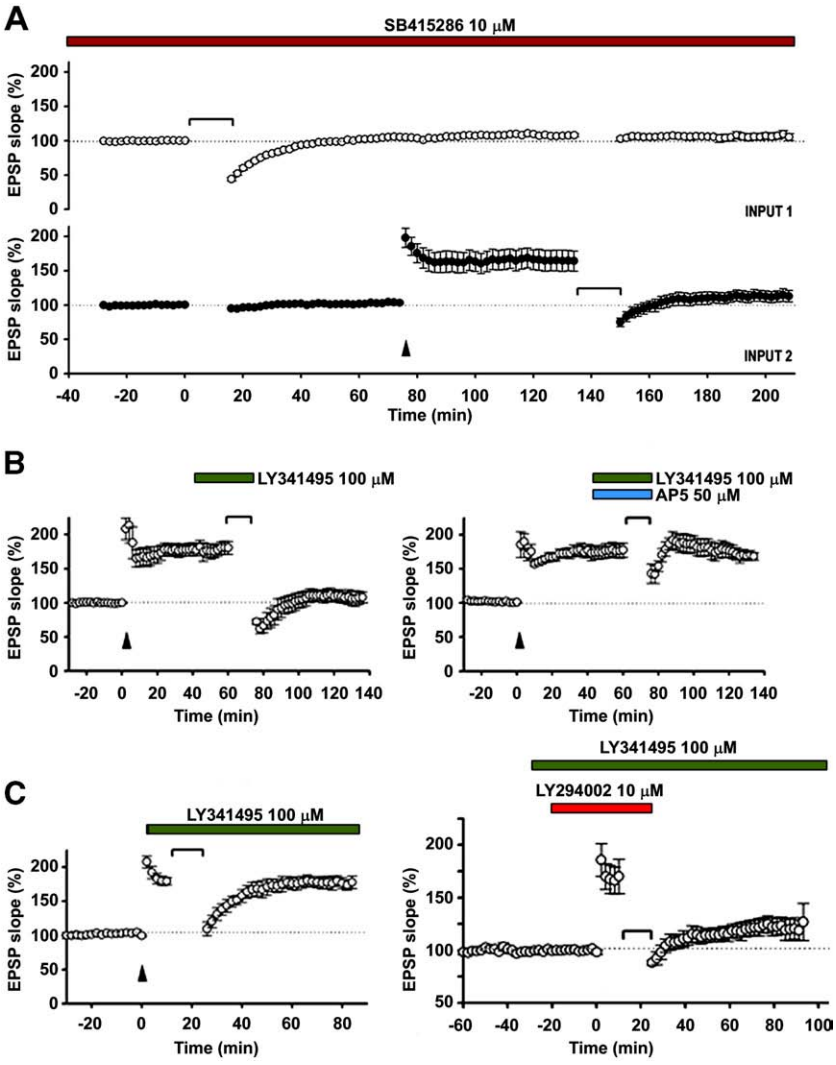


Fig. 7. Long-term potentiation inhibits long-term depression via regulation of glycogen synthase kinase-3. (A) The glycogen synthase kinase-3 inhibitor, SB415286, blocks the induction of long-term depression (input 1) but not long-term potentiation or depotentiation (input 2). (B) Long-term potentiation (induced at $t=0$) is reversed by low frequency stimulation deliverd 1 h later, in an NMDA receptor-dependent manner. LY341495 was present to block mGlu receptor-dependent plasticity. (C) The same stimuli delivered shortly following the tetanus failed to reverse long-term potentiation because long-term potentiaiton inhibits NMDA receptor-dependent long-term depression. This block of long-term depression is inhibited by the PI3K inhibitor LY294002. Data from Peineau et al., 2007.

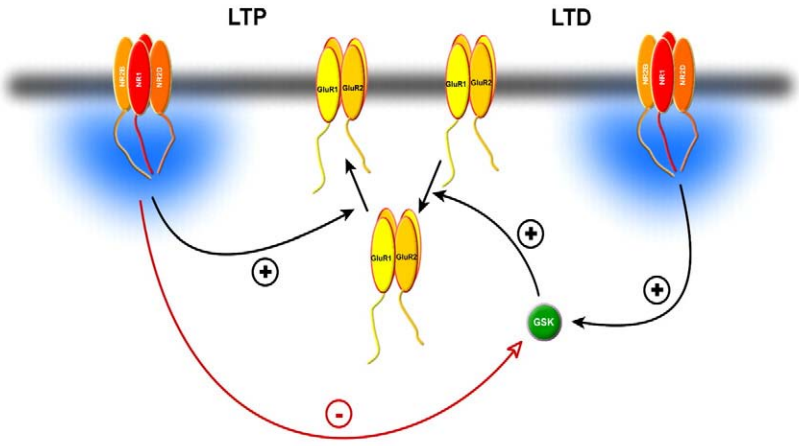


Fig. 8. Long-term potentiation inhibits long-term depression via regulation of glycogen synthase kinase-3. Long-term potentiation drives AMPA receptors into synapses whilst long-term depression causes their removal. The activation of glycogen synthase kinase-3 is a key component of the long-term depression mechanism. Long-term potentiation inhibits long-term depression, via the PI3K-Akt pathway. A loss of long-term potentiation, that may occur during the development of Alzheimer's disease, could lead to a reduction in the inhibitory regulation of glycogen synthase kinase-3. This could result in hyperphosphorylation of downstream effectors, such as tau.

synaptic plasticity to occur when there is sufficient activation of NMDA receptors. By virtue of its voltage-dependent and relatively low affinity block of NMDA receptors it will be rapidly expelled from NMDA receptors during the hebbian depolarisation.

5. A role for glycogen synthase kinase-3 in synaptic plasticity

Another way in which the hippocampal slice preparation may be useful in understanding the aetiology of Alzheimer's disease is in determining the function of enzymes implicated in the disease. If the normal function(s) are known then the pathological roles may be easier to understand and intervention may be more readily achieved. By way of an example is glycogen synthase kinase-3. This enzyme is strongly implicated in Alzheimer's disease, where it hyperphosphorylates tau (hence is also known as tau kinase; (Bhat et al., 2004; Grimes and Jope, 2001).

We have recently shown that its activation is required for NMDA receptor-dependent long-term depression in the hippocampus (Fig. 7A; Peineau et al., 2007). Conversely, overexpression of glycogen synthase kinase-3β results in inhibition of NMDA receptor-dependent long-term potentiation (Hooper et al., 2007). Thus, glycogen synthase kinase-3 activity is "good" for long-term depression and "bad" for long-term potentiation. Glycogen synthase kinase-3 provides a mechanism to enable cross-talk between long-term potentiation and long-term depression. The induction of long-term potentiation results in inhibition of glycogen synthase kinase-3, via the PI3K-Akt pathway, and this prevents the induction of NMDA receptor-dependent long-term depression for up to about 1h (Fig. 7B,C).

The downstream substrates for glycogen synthase kinase-3 that are involved during long-term depression are currently unknown. It is tempting to speculate however that one of these could be tau. During long-term depression the phosphorylation of tau might be involved in the alterations in spine morphology that accompanies long-term depression. Excessive long-term depression could perhaps result in hyperphosphorylation of tau. Alternatively dysregulation of glycogen synthase kinase-3 might result. Perhaps when long-term potentiation fails, the break on glycogen synthase kinase-3 activity is removed? This idea is shown schematically in Fig. 8. Clearly, much work is needed to understand the pathological function of glycogen synthase kinase-3 in Alzheimer's disease but knowing how it is involved in synaptic plasticity at least provides testable theoretical frameworks.

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