Bidirectional plasticity expressed by GABAergic synapses in the neonatal rat hippocampus

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1. Activity-dependent plasticity of GABAergic synaptic transmission was investigated in neonatal rat hippocampal slices obtained between postnatal day (P) 2–10 using intracellular recording techniques. In all experiments, AMPA receptors were blocked by continual application of CNQX (10 μM).

2. Between P2 and P4, tetanic stimulation (TS) evoked NMDA receptor-dependent long-term depression of monosynaptic $GABA_A$ EPSPs (LTD_{GABA_A}). In contrast, when NMDA receptors were blocked by D-AP5 (50 μM), the same TS evoked long-term potentiation of $GABA_A$ EPSPs (LTP_{GABA_A}).

3. Between P6 and P10, TS failed to produce either LTP or LTD of hyperpolarizing monosynaptic $GABA_A$ IPSPs under the same recording conditions. However, when GABAergic potentials were rendered depolarizing (KCl-filled electrode) TS induced either LTP_{GABA_A} or LTD_{GABA_A} in the presence or absence of D-AP5, respectively.

4. Both LTP_{GABA_A} and LTD_{GABA_A} were specific to the conditioned pathway and could be sequentially expressed at the same synapses. Potentiation of GABAergic synaptic efficacy was induced more easily following previous induction of LTD_{GABA_A} than in naive slices.

5. In conclusion, early in development, bidirectional synaptic plasticity is expressed by $GABA_A$ receptors and the activation (or not) of NMDA receptors determines the induction of either LTP_{GABA_A} or LTD_{GABA_A}.

Activity-dependent synaptic plasticity may underlie seemingly diverse phenomena such as learning and memory and the maturation of neuronal networks, and may also be involved in the manifestation of pathophysiological conditions such as epilepsy and ischaemia. The now classical model for studies of synaptic plasticity in adult tissue is long-term potentiation (LTP) and long-term depression (LTD) of excitatory glutamatergic transmission. In the hippocampus, LTP is usually induced by high frequency train stimulation (tetanic stimulation) or by a pairing protocol involving presynaptic afferent stimulation and postsynaptic membrane depolarization, whereas induction of LTD requires low frequency train stimulation (Bear & Malenka, 1994). The same synapse can often be potentiated or depressed depending on the stimulation protocol employed (Dudek & Bear, 1993). In spite of their different induction protocols, both LTP and LTD are expressed primarily by AMPA receptors, and triggered by calcium influx via NMDA receptor–channels or voltage-dependent calcium channels (VDCCs) (Aniksztejn & Ben-Ari, 1991; Bear & Malenka, 1994). It is widely believed that the magnitude of calcium influx determines the change in direction of synaptic efficacy, i.e. potentiation or depression (Artola & Singer, 1993; Bear & Malenka, 1994).

In the neonatal hippocampus, glutamatergic LTP is not readily observed until P14 (Harris & Teyler, 1984; Dudek & Bear, 1993) and LTD has not been revealed earlier than P6 (Dudek & Bear, 1993; Bolshakov & Siegelbaum, 1994). In addition, GABA, acting via $GABA_A$ receptors, provides the main excitatory drive to neonatal hippocampal neurones (Ben-Ari, Cherubini, Corradetti & Gaiarsa, 1989; Fizman, Novotny, Lange & Barker, 1990), while AMPA receptors are quiescent until postnatal day 4 or 5 (Durand, Kovalchuk & Konnerth, 1996). Keeping in mind that at this early age, $GABA_A$ receptor activation also increases intracellular calcium concentration via NMDA channels (Ben-Ari, Khazipov, Khalilov & Leinekugel, 1996) and VDCCs (Leinekugel, Tseeb, Ben-Ari & Bregestovski, 1995), we reasoned that GABAergic synapses may be the target for LTP and LTD expression at early stages of development.

In the present study, we show that input-specific LTP and LTD of monosynaptic GABAergic potentials are expressed by $GABA_A$ receptors at early stages of development in the

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rat hippocampus. These phenomena are hereafter referred to as LTP_{GABA_A} and LTD_{GABA_A}, respectively. LTP_{GABA_A} and LTD_{GABA_A} induction requires $GABA_A$ receptor activation and a rise in intracellular calcium. However, whereas LTD_{GABA_A} is induced by the synergistic activation of $GABA_A$ and NMDA receptors, LTP_{GABA_A} is only observed when NMDA receptors are blocked.

METHODS

Experiments were performed on hippocampal CA3 pyramidal neurones obtained from Wistar rats, postnatal day 3–10 (P3–P10). Brains were removed under ether anaesthesia and submerged in artificial cerebrospinal fluid (ACSF; mM): NaCl, 126; KCl, 3·5; $CaCl_2$, 2; $MgCl_2$, 1·3; NaH_2PO_4, 1·2; $NaHCO_3$, 25; and glucose, 11; pH 7·4 when equilibrated with 95% O_2–5% CO_2. Hippocampal slices, 600 μm thick, were cut with a McIlwain tissue chopper and incubated in ACSF at room temperature (20–23 °C) for at least 60 min before use. Individual slices were then transferred to a submerged recording chamber and superfused with ACSF at 2·5–3 ml min^{-1} at 34 °C.

Intracellular recordings of CA3 pyramidal neurones were performed using an Axoclamp-2 amplifier. Pipette solution contained 50 mM 2(triethylamino)-*N*-(2,6-dimethylphenyl) acetamine (QX-314; to block $GABA_B$ IPSPs) dissolved in either 2 M $KMeSO_4$ or 3 M KCl. Neurones that were accepted for analysis had membrane potentials more negative than −50 mV and stable input resistances greater than 60 MΩ. In some experiments, BAPTA (50 mM) was dissolved in 3 M KCl and iontophoresed intracellularly with suprathreshold depolarizing current pulses (500 ms, 10–30 min). Cells were considered to be BAPTA-loaded when they showed neither spike-frequency accommodation nor after-hyperpolarization following a suprathreshold depolarizing pulse (500 ms, 400 pA).

Electrical stimulation (30–60 μs, 10–30 V, 0·03 Hz) was performed with a bipolar tungsten electrode (50 μm diameter) positioned in the hilus. For some experiments (the S1/S2 series) a second stimulating electrode was positioned in the stratum oriens close to the fimbria. Tetanic stimuli (TS; 3 trains; 100 Hz, 1 s) were delivered at 30 s intervals from a resting membrane potential of −60 mV. The intensity of test and tetanic stimuli were 2 and 3 times the threshold required to elicit $GABA_A$ postsynaptic potentials, respectively. Changes in the slope of $GABA_A$ postsynaptic potentials were expressed as a percentage of control values. Data are presented as means ± S.E.M. Statistical analysis was performed using Student's paired *t* test. Data were judged to differ when $P < 0{\cdot}05$. Drugs used were: 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX: Tocris); D(−)2-amino-5-phosphovaleric acid (D-AP5; Tocris), bicuculline (Tocris) and BAPTA (Molecular Probes); all were dissolved in ACSF and bath applied.

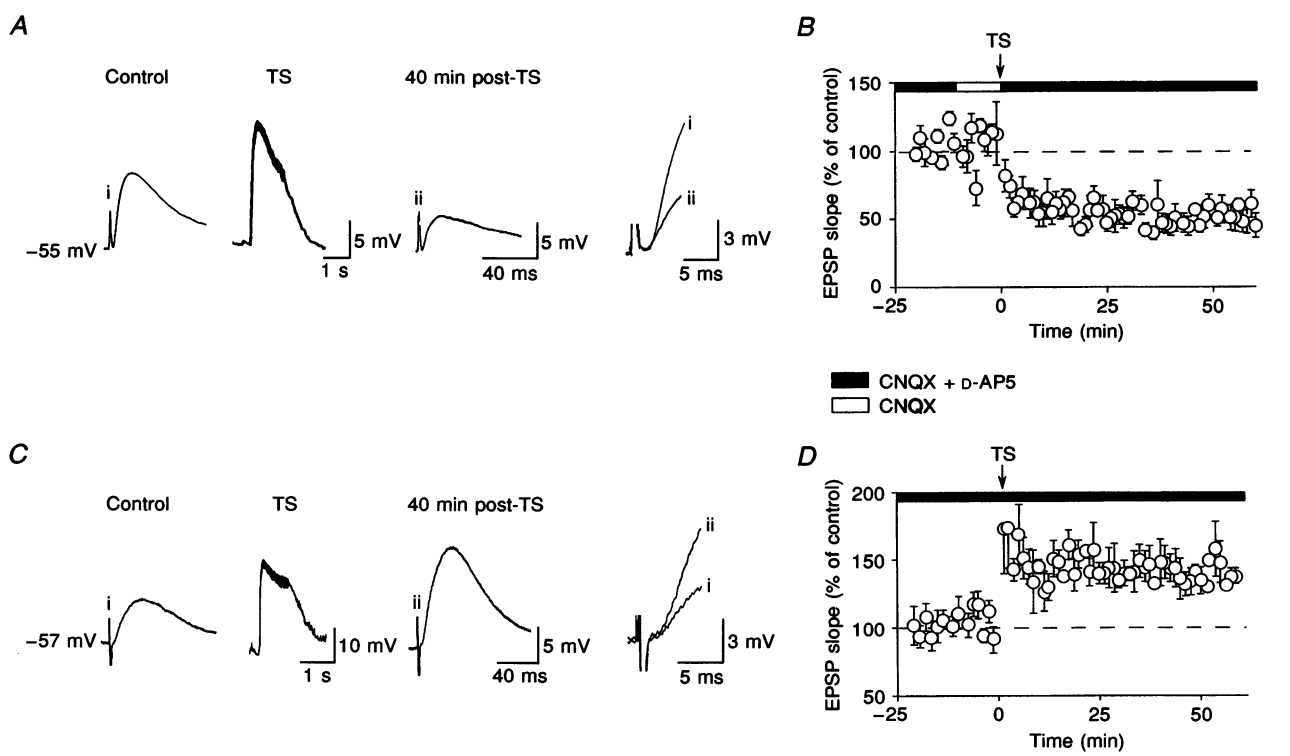

Figure 1. LTD and LTP of $GABA_A$ EPSPs between P2 and P4

A, evoked $GABA_A$-mediated EPSPs recorded at P3 ($KMeSO_4$-filled electrode) in CNQX (10 μM) and D-AP5 (50 μM), before (i) and 40 min after (ii) tetanic stimulation (TS) applied in CNQX alone. Superimposed GABA EPSPs (far right trace) show a clear decrease in initial slope following TS. *B*, time course of changes in GABA EPSP slope following TS ($n = 6$). *C*, evoked $GABA_A$-mediated EPSPs recorded at P3 ($KMeSO_4$-filled electrode) before (i) and 40 min after (ii) TS applied in CNQX and D-AP5. Superimposed GABA EPSPs (far right trace) show a clear increase in initial slope following TS. *D*, time course of changes in GABA EPSP slope following TS ($n = 5$). In this and the following figures, EPSPs/IPSPs represent an average of 15 traces and TS was applied at a membrane potential of −60 mV.

RESULTS

Evoked monosynaptic $GABA_A$ receptor-mediated postsynaptic potentials were isolated in the presence of CNQX (10 μM) and D-AP5 (50 μM) (Ben-Ari *et al.* 1989; McLean, Rovira, Ben-Ari & Gaiarsa, 1995). With $KMeSO_4$ pipette solution, CA3 pyramidal neurones exhibited depolarizing GABAergic postsynaptic potentials (GABA EPSPs) between postnatal day 2 and 4 (P2–P4) (Fig. 1*A*) and hyperpolarizing GABAergic postsynaptic potentials (GABA IPSPs) between P6 and P10 (Fig. 2*A*). GABA EPSPs and IPSPs were reversibly blocked by bicuculline (10 μM) and thus mediated by $GABA_A$ receptors (data not shown but see Ben-Ari *et al.* 1989; McLean *et al.* 1995). After a control period, D-AP5 was washed, and three trains of TS (100 Hz, 1 s) were delivered at 30 s intervals in CNQX (10 μM). D-AP5 was then reintroduced to isolate test GABAergic potentials.

At P2–P3, TS evoked a mean membrane depolarization of 15 ± 7 mV ($n = 6$; Fig. 1*A*). Within 10 min after TS the slope of test GABA EPSPs was depressed for at least 60 min (49 ± 3% of control value, $P = 0{\cdot}0001$, $n = 6$) in six out of seven neurones (Fig. 1*A* and *B*) without any change in their reversal potential (-41 ± 2 mV *versus* -40 ± 5 mV, $P = 0{\cdot}78$, $n = 6$), membrane input resistance ($90{\cdot}5 \pm 11$ MΩ *versus* 91 ± 12 MΩ, $P = 0{\cdot}40$, $n = 6$), or EPSP onset latency. This LTD of evoked monosynaptic $GABA_A$-mediated postsynaptic potentials is hereafter referred to as LTD_{GABA_A}.

Since most forms of glutamatergic synaptic plasticity are dependent on the activation of NMDA receptors (Bear & Malenka, 1994), we examined the NMDA receptor dependence of LTD_{GABA_A}. In the presence of CNQX and D-AP5, TS produced a membrane depolarization of 13 ± 3 mV, but failed to induce LTD_{GABA_A} (114 ± 10%,

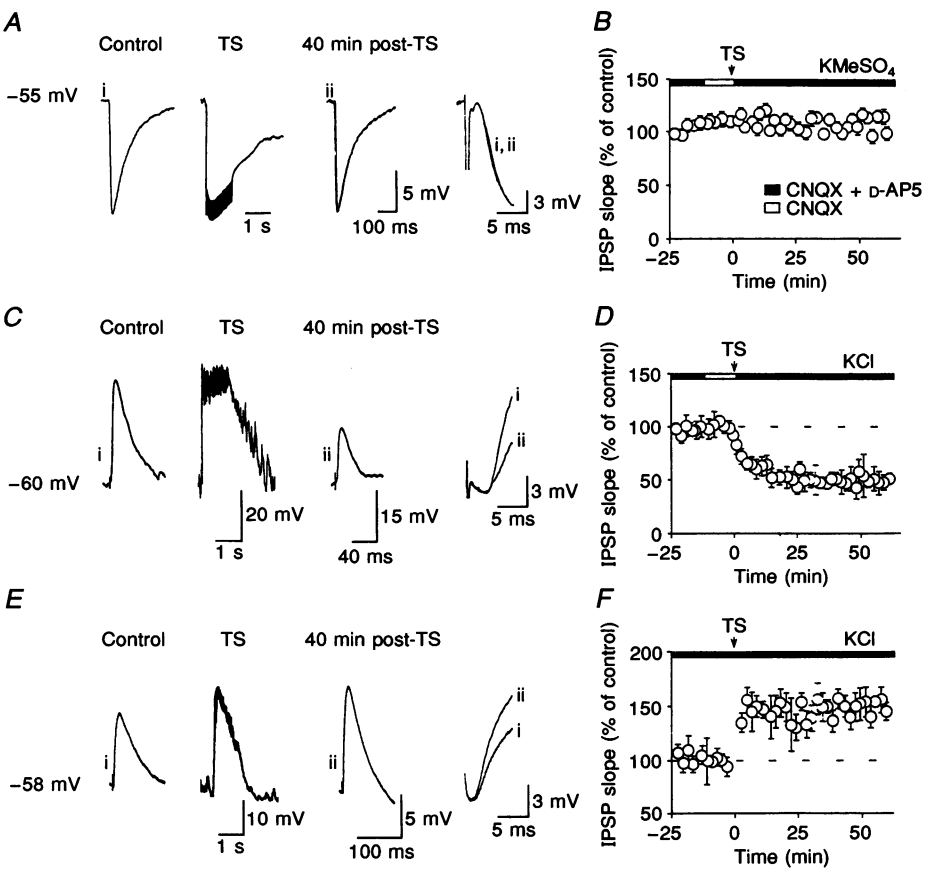

Figure 2. LTD_{GABA_A} and LTP_{GABA_A} are revealed between P6 and P10 with an inverted transmembrane gradient to chloride ions

A, evoked $GABA_A$-mediated IPSPs recorded at P6 ($KMeSO_4$-filled electrode) in CNQX (10 μM) and D-AP5 (50 μM), before (i) and 40 min after (ii) TS applied in CNQX alone. Superimposed GABA IPSPs (far right trace) show no change in initial slope following TS. *B*, time course of changes in GABA IPSP slope following TS ($n = 5$). *C*, evoked $GABA_A$-mediated IPSPs recorded at P6 (KCl-filled electrode) before (i) and 40 min after (ii) TS applied in CNQX alone. Superimposed GABA IPSPs (far right trace) show a clear decrease in initial slope following TS. *D*, time course of changes in GABA IPSP slope following TS ($n = 10$). *E*, evoked $GABA_A$-mediated IPSPs recorded at P6 (KCl-filled electrode) before (i) and 40 min after (ii) TS applied in CNQX and D-AP5. Superimposed GABA IPSPs (far right trace) show a clear increase in initial slope following TS. *F*, time course of changes in GABA IPSP slope following TS ($n = 10$).

$P = 0{\cdot}16$, $n = 5$) in five out of nine neurones. In the four remaining neurones, the same TS induced a persistent and long lasting ($\geqslant 60$ min) increase in the slope of GABA EPSPs ($142 \pm 5\%$ of control value, $P = 0{\cdot}0001$; Fig. 1*C* and *D*), with no change in membrane input resistance (78 ± 11 MΩ *versus* 75 ± 5 MΩ, $P = 0{\cdot}6$, $n = 4$). This LTP of evoked monosynaptic $GABA_A$-mediated postsynaptic potentials is hereafter referred to as LTP_{GABA_A}.

For the most part, induction of changes in synaptic efficacy requires postsynaptic membrane depolarization which allows for activation of VDCCs, or for release of the magnesium block of NMDA receptor–channels (Bear & Malenka, 1994). In our study, this depolarization is generated by the activation of $GABA_A$ receptors since bath application of bicuculline (10 μM) during TS prevented membrane depolarization (-2 ± 2 mV in CNQX and bicuculline, $n = 6$; $1{\cdot}8 \pm 2$ mV in CNQX, D-AP5 and bicuculline, $n = 4$) and the induction of LTD_{GABA_A} (initial slope = $102 \pm 8\%$ of control value, $n = 6$) and LTP_{GABA_A} (initial slope = $105 \pm 3\%$ of control value, $n = 4$). These data therefore suggest that $GABA_A$ receptor-mediated postsynaptic depolarization is necessary to induce LTD_{GABA_A} and LTP_{GABA_A}.

In keeping with this idea, with $KMeSO_4$ pipette solution, both LTP_{GABA_A} and LTD_{GABA_A} were restricted to a critical period of development (P2–P4) when activation of $GABA_A$ receptors induced membrane depolarization. Between P6 and P10, TS in CNQX evoked an average membrane hyperpolarization of -15 ± 2 mV ($n = 5$; Fig. 2*A* and *B*) and did not affect the slope of test GABA IPSPs ($114 \pm 10\%$ of control value, $P = 0{\cdot}16$, $n = 5$; Fig. 2*A* and *B*). However, when GABA IPSPs were rendered depolarizing by reversing the transmembrane gradient to chloride ions with KCl-filled electrodes, the same TS produced a membrane depolarization (22 ± 10 mV) followed by LTD_{GABA_A} (slope = $55 \pm 17\%$ of control value, $P = 0{\cdot}0001$, $n = 10$) in ten out of fourteen neurones (Fig. 2*C* and *D*). LTD_{GABA_A} induced under these conditions was also NMDA receptor dependent since TS in CNQX and D-AP5 had no effect on the slope of test GABAergic monosynaptic potentials ($102 \pm 7\%$ of control

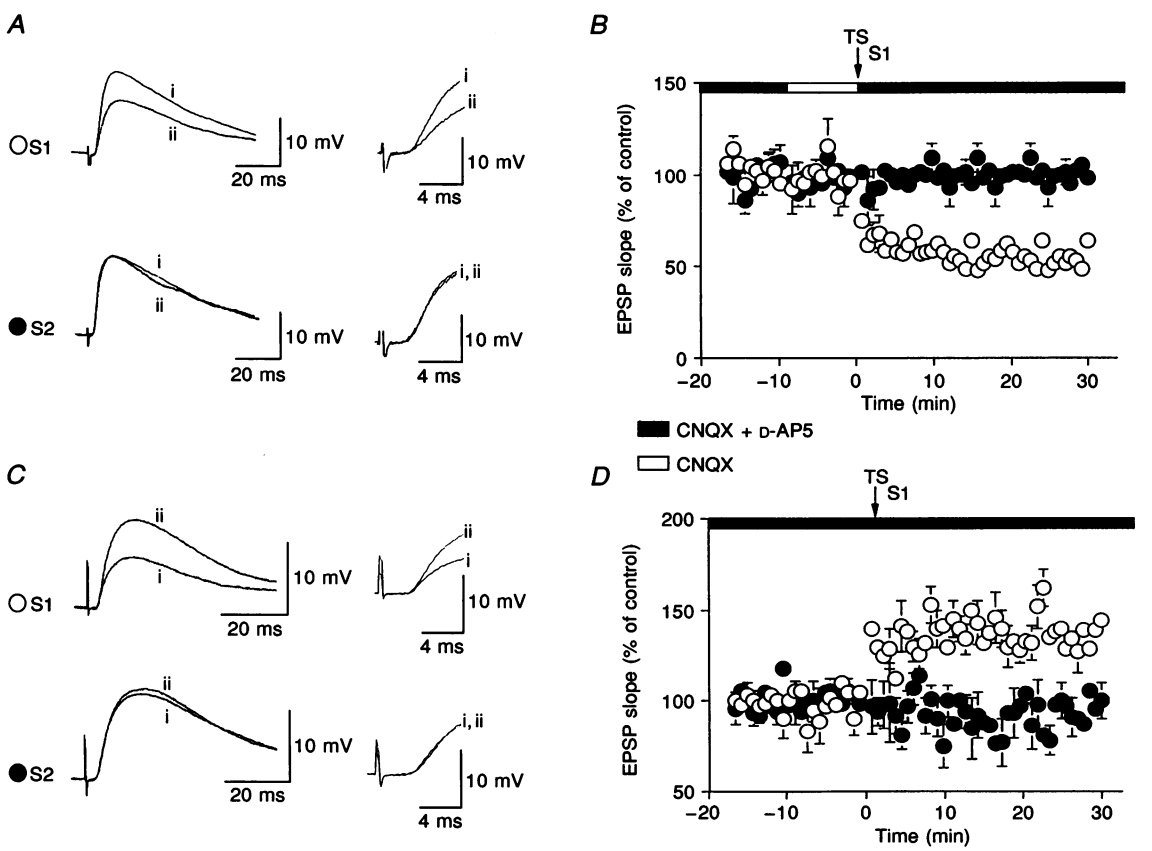

Figure 3. LTD_{GABA_A} and LTP_{GABA_A} are homosynaptic

A, superimposed $GABA_A$-mediated EPSPs recorded at P3 ($KMeSO_4$-filled electrode) in CNQX (10 μM) and D-AP5 (50 μM), before (i) and 30 min after (ii) TS in CNQX. S1 (conditioned pathway) stimulating electrode in the hilus, S2 (unconditioned pathway) stimulating electrode in the fimbria. Superimposed GABA EPSPs (right traces) show a clear decrease in initial slope following TS only in S1. *B*, time course of changes in GABA EPSP slope following TS ($n = 4$). *C*, superimposed $GABA_A$-mediated EPSPs recorded at P3 ($KMeSO_4$-filled electrode) in CNQX and D-AP5, before (i) and 30 min after (ii) TS in CNQX and D-AP5. Superimposed GABA EPSPs (right traces) show a clear increase in initial slope following TS only in S1. *D*, time course of changes in GABA EPSP slope following TS ($n = 3$).

value, $P = 0{\cdot}88$, $n = 10$) in ten out of twenty neurones. In the remaining neurones, TS in CNQX and D-AP5 produced a membrane depolarization (25 ± 8 mV) followed by LTP_{GABA_A} ($150 \pm 2{\cdot}3\%$ of control value, $P = 0{\cdot}0001$, $n = 10$; Fig. 2*E* and *F*).

As with most forms of plasticity at glutamatergic synapses (Artola & Singer, 1993; Bear & Malenka, 1994), the induction of both LTP_{GABA_A} and LTD_{GABA_A} require a rise in intracellular calcium. When neurones were loaded with the calcium chelator BAPTA (50 mM), TS in CNQX and D-AP5 failed to induce LTP_{GABA_A} ($104 \pm 22\%$ of control value 30 min after TS, $n = 5$). Similarly, following TS in CNQX alone, BAPTA-loaded neurones failed to exhibit LTD_{GABA_A} ($103 \pm 7\%$ of control value 30 min after TS, $n = 7$).

LTP_{GABA_A} and LTD_{GABA_A} share other properties with long-term modifications of glutamatergic synaptic transmission in adult tissue, namely, both LTP_{GABA_A} and LTD_{GABA_A} are homosynaptic and can be sequentially induced at the same synapses. Figure 3 shows that LTP_{GABA_A} and LTD_{GABA_A} were specific to the conditioned synapses. Two independent groups of GABAergic fibres were stimulated alternatively and TS was applied with one of the stimulating electrodes placed in either the hilus or the fimbria (S1). After TS in CNQX alone, the slope of the GABA EPSPs in the conditioned pathway (S1) decreased to a value that stabilized at $54 \pm 5\%$ of control value ($n = 4$), while the GABA EPSPs, evoked by way of the unconditioned pathway placed in either the fimbria or the hilus (S2), remained unchanged ($100 \pm 4\%$ of control value; Fig. 3*A* and *B*). Similarly, following TS in CNQX and D-AP5 the slope of the GABA EPSPs increased only in the conditioned pathway (S1) ($142 \pm 5\%$ *versus* $98 \pm 6\%$, $P = 0{\cdot}001$, $n = 3$; Fig. 3*C* and *D*). Results were identical when the S1 electrode was placed in the hilus and the S2 electrode in the fimbria as when the S1 electrode was placed in the fimbria and the S2 electrode in the hilus.

LTP_{GABA_A} and LTD_{GABA_A} were sequentially induced at the same synapses. As illustrated in Fig. 4*A*, TS in CNQX and D-AP5 resulted in LTP_{GABA_A}, with the slope of GABA EPSPs potentiated to $154 \pm 6\%$ of control values ($n = 2$). A subsequent TS in CNQX alone resulted in depotentiation of $GABA_A$ responses, with the slope of GABA EPSPs reduced to $50{\cdot}6 \pm 2{\cdot}8\%$ of values taken after the first TS. Similarly, following induction of LTD_{GABA_A} by TS in CNQX (slope $= 46 \pm 3\%$ of control values, $P = 0{\cdot}0001$, $n = 4$), TS

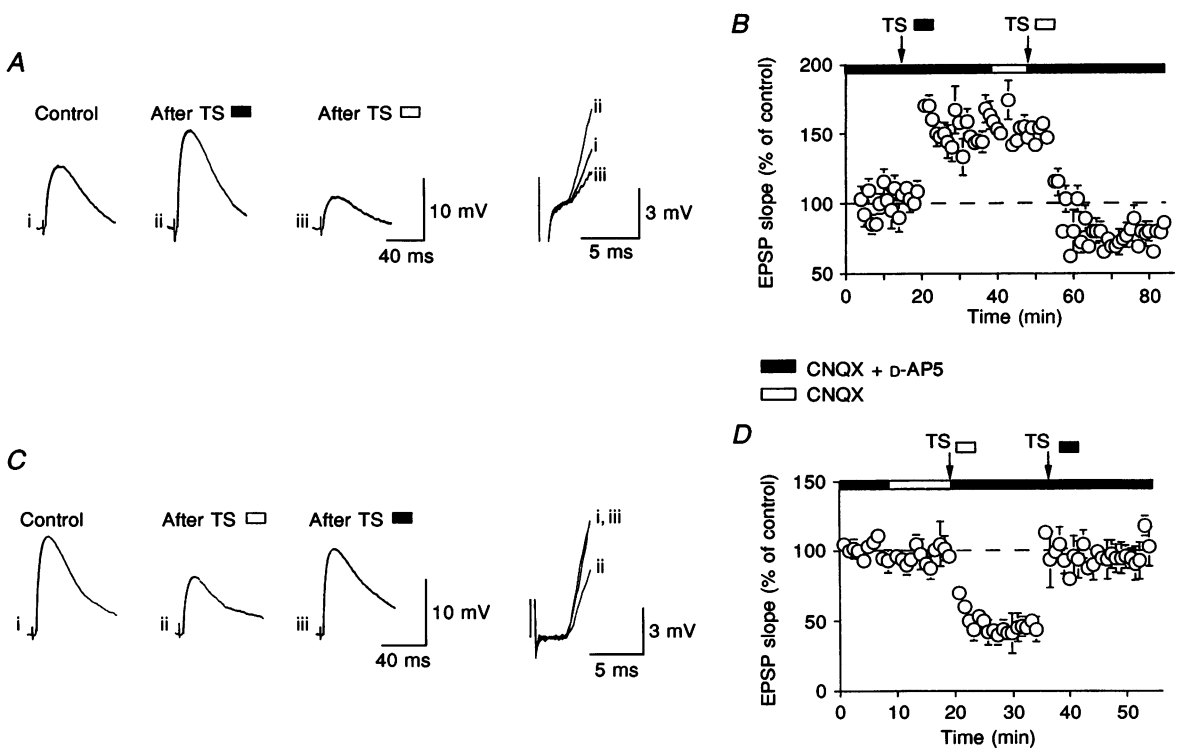

Figure 4. Potentiation and depression expressed at the same synapses

A, evoked $GABA_A$-mediated EPSPs recorded at P3 ($KMeSO_4$-filled electrode) in CNQX (10 μM) and D-AP5 (50 μM) before (i), 20 min after TS applied in CNQX and D-AP5 (ii) and 20 min after TS applied in CNQX (iii). Superimposed GABA EPSPs (far right trace) show a clear increase (i,ii) and decrease (ii,iii) in initial slope following TS. *B*, time course of changes in GABA EPSP slope following TS ($n = 2$). *C*, evoked $GABA_A$-mediated EPSPs recorded at P3 ($KMeSO_4$-filled electrode) in CNQX (10 μM) and D-AP5 (50 μM) before (i), 20 min after TS applied in CNQX (ii) and 20 min after TS applied in CNQX and D-AP5 (iii). Superimposed GABA EPSPs (far right trace) show a clear decrease (i,ii) and increase (ii,iii) in initial slope following TS. *D*, time course of changes in GABA EPSP slope following TS ($n = 4$).

in CNQX and D-AP5 potentiated $GABA_A$ responses (slope = 215 ± 10% of values taken after the first TS, $P = 0.0001$, $n = 4$). Interestingly, while TS in CNQX and D-AP5 induced LTP_{GABA_A} in 45% of naive slices (Figs 1 and 2), following induction of LTD_{GABA_A}, subsequent potentiation of $GABA_A$ responses was successful in four out of four cells. As proposed for glutamatergic synapses (Bear & Malenka, 1994), these observations suggest that $GABA_A$ synapses are in a near fully potentiated state at a very early stage of postnatal development.

DISCUSSION

The principal conclusions of this study are: (i) during the first few postnatal days of life, $GABA_A$ synapses express long-term potentiation and long-term depression (LTP_{GABA_A} and LTD_{GABA_A}, respectively); (ii) the induction of both LTP_{GABA_A} and LTD_{GABA_A} require a $GABA_A$ receptor-mediated membrane depolarization and an increase in intracellular calcium during TS; and (iii) the same TS induces either LTD_{GABA_A} or LTP_{GABA_A}, depending on whether or not NMDA receptors are activated, respectively.

Similarities and differences between GABAergic plasticity in neonates and glutamatergic plasticity in adults

LTP_{GABA_A} and LTD_{GABA_A} observed in the neonatal hippocampus share common properties with long-term modifications of glutamatergic synaptic transmission in adult preparations (Bear & Malenka, 1994). Namely, LTP_{GABA_A} and LTD_{GABA_A} were specific to the conditioned pathway and could be sequentially expressed at the same synapses. Similarly, the induction of LTP_{GABA_A} and LTD_{GABA_A} required an initial membrane depolarization. Indeed, LTP_{GABA_A} and LTD_{GABA_A} were observed only when $GABA_A$ postsynaptic potentials were either naturally (P2–P4, $KMeSO_4$ electrodes) or artificially (P6–P10, KCl electrodes) depolarizing. All of our experiments were performed in CNQX, which ensured that once functional (around P4; see Durand *et al.* 1996) AMPA receptors did not participate in the induction of GABAergic synaptic plasticity. These observations, along with the blockade of LTD and LTP by bicuculline, suggest that a key inductive factor is $GABA_A$ receptor-mediated membrane depolarization during TS. In addition, we provide evidence that the induction of both LTP_{GABA_A} and LTD_{GABA_A} requires an increase in the postsynaptic calcium concentration, since neither of these phenomena were observed in neurones loaded with the calcium chelator BAPTA.

However, an important difference exists between the induction of glutamatergic plasticity in adults and the induction of GABAergic plasticity in neonates described in this study. In adults, both glutamatergic LTP and LTD are NMDA receptor dependent, require different stimulation protocols for their induction (Bear & Malenka, 1994), and it seems to be the magnitude of the intracellular calcium influx during stimulation that ultimately determines the direction of plasticity (Bear & Malenka, 1994). In our study, LTP and LTD were both triggered by the same tetanic stimulation, and the direction of plasticity was determined by the activation (or not) of NMDA receptors during the tetanus. Given that both LTD_{GABA_A} and LTP_{GABA_A} are calcium dependent, these observations suggest that the principal source of calcium influx for the induction of LTD_{GABA_A} and LTP_{GABA_A} is different (i.e. NMDA receptor–channels *versus* VDCCs). Alternatively, as has been suggested for glutamatergic synapses (Bear & Malenka, 1994), perhaps it is a difference in the level of intracellular calcium increases stemming from the activation of VDCCs alone in the case of LTP_{GABA_A} or VDCCs plus NMDA receptors in the case of LTD_{GABA_A}.

Similarities and differences in GABAergic plasticity between neonates and adults

The present study is the first description of GABAergic synaptic plasticity in the neonatal hippocampus. Several recent studies have demonstrated both short- and long-term changes in GABAergic synaptic transmission in the adult central nervous system. In the cerebellum, rises in intracellular calcium levels lead to a transient depression of $GABA_A$ inhibitory postsynaptic currents, IPSCs, (Marty & Llano, 1995) followed by long lasting potentiation of spontaneous $GABA_A$ IPSCs, termed 'rebound potentiation' by Kano and co-workers (Kano, Rexhausen, Dreessen & Konnerth, 1992). Short-term depression of $GABA_A$ IPSCs following postsynaptic membrane depolarization has also been described in CA1 pyramidal neurones of the hippocampus (Pitler & Alger, 1992), and appears to be mediated presynaptically, and possibly involves a retrograde messenger (Marty & Llano, 1995). In contrast, the persistent rebound potentiation appears to be mediated postsynaptically since it is associated with an increase in membrane responses to exogenous GABA (Kano *et al.* 1992).

In CA1 pyramidal neurones of the hippocampus, long lasting depression of GABAergic IPSPs has been observed following TS that generates paroxysmal activity (Stelzer, Slater & ten Bruggencate, 1987). More recently, Stelzer and co-workers (Stelzer, Simon, Kovacs & Rai, 1994; Wang & Stelzer, 1996) have suggested that LTP of glutamatergic synapses following tetanic stimulation is partly due to concomitant LTD of GABAergic synapses. However, this LTD of GABAergic transmission is observed only in dendritic, not somatic, recordings and its induction probably involves the activation of AMPA receptors during the tetanus. This is in contrast to our study where LTD_{GABA_A} was observed in somatic recordings, but did not involve AMPA receptors; the initial membrane depolarization for its induction being mediated by the activation of $GABA_A$ receptors.

Both LTP and LTD of GABA IPSPs have been observed in the visual cortex of young (P20–P30) rats (Komatsu & Iwakiri, 1993; Komatsu, 1994). However, there are important differences between these studies and the present

work. Specifically, in contrast to the neonatal hippocampus, the visual cortex LTP induction did not require membrane depolarization. In addition, in the neonatal hippocampus, LTD induction required that $GABA_A$ and NMDA receptors work in synergy, while in the visual cortex LTD was only observed when $GABA_A$ receptors were blocked by bicuculline.

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