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Reduced long-term potentiation in the dentate gyrus of $mGlu_1$ receptor-mutant mice in vivo

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Abstract

Long-term potentiation in the dentate gyrus was studied in vivo in mutant mice lacking the metabotropic glutamate (mGlu) subtype 1 receptor. Long-term potentiation was induced in wild type animals ($n = 7$), but was reduced in mice lacking this receptor subtype ($n = 7$). These data suggest that mGlu receptors may be involved in the induction or maintenance of synaptic plasticity or that these receptors are required during development to establish this plasticity.

Keywords: Long-term potentiation; Mutant mouse; Glutamate receptor, metabotropic

It is generally accepted that long-term potentiation requires the activation of post-synaptic NMDA receptors. The metabotropic glutamate (mGlu) receptors have also been implicated in the induction of long-term potentiation in the hippocampus (Bashir et al., 1993), although pharmacological evidence that these receptors are required is still lacking (Selig et al., 1995). Recently, we (Conquet et al., 1994) and others (Aiba et al., 1994) examined long-term potentiation in hippocampal slices from mice lacking the $mGlu_1$ receptor subtype, but these studies left open the role of these receptors in long-term potentiation in vivo (Malenka, 1994). In the present study this question was addressed directly by measuring long-term potentiation in vivo in dentate gyri from $mGlu_1$ receptor mutant (−/−) mice. We found that long-term potentiation is reduced in the mutant mice compared to wild type (+/+) controls.

Male mice lacking (−/−) $mGlu_1$ receptor ($n = 7$) and with normal (+/+) $mGlu_1$ receptor ($n = 7$) obtained from the Glaxo Institute of Molecular Biology (Geneva, Switzerland) weighing 18–27 g were anesthetized with urethane (1.2 g/kg body weight) and placed in a Kopf stereotaxic frame. Body temperature was regulated at 37°C ± 1 by means of a heating pad. A bipolar stimulating electrode (tip diameter 150 μm) was placed in the perforant path (AP 0.5 mm anterior to lambda, ML 2.5 mm to mid-line, DV 1.7–2.2 mm to brain surface) and evoked potentials were recorded extracellularly with a stainless steel electrode (1–2 MΩ impedance) from the cell body layer of the ipsilateral dentate gyrus (AP −2.0 mm from bregma, ML 1.0 mm, DV 1.7–2.2 mm to brain surface). Both electrodes were driven ventrally using hydraulic micropositioners to search for the best location and optimize the amplitude of the population spike obtained with test pulses. Neural potentials were amplified, band-pass filtered (2–2000 Hz) and recorded digitally on a personal computer (Axobasic system, Axon Instruments). Test pulses (0.1 ms duration, 0.033 Hz, 100–300 μA) were applied for at least 30 min prior to tetanic stimulation at a level sufficient to evoke a population spike amplitude of about 1/3 maximum. Tetanus (three trains, 10 s apart, 400 Hz, eight 0.4 ms impulses in each train; Numgung et al., 1995) was applied at the same intensity of the test pulse. Recordings of the evoked potential continued for 1–2 h after tetanization. Waveforms were analyzed as described previously (Bordi and Ugolini, 1995).

There was a similar laminar profile of the recorded potential in normal and mutant mice, both in dendritic layers and in the dentate granular cell layer (not shown). In all seven $mGlu_1$ receptor +/+ mice tetanic stimulation resulted in a clear potentiation of population spike amplitude recorded for 1–2 h post-tetanus (Fig. 1A). In the seven $mGlu_1$ receptor −/− mice, on the other hand, long-term potentiation was significantly less ($P < 0.05$, t test) than control at 1 h post-tetanus. There was no statisti-

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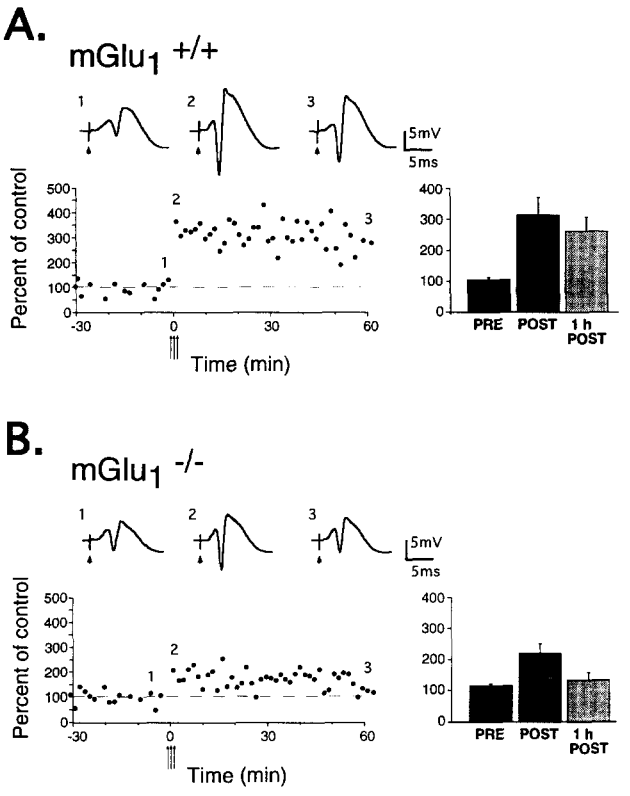

Fig. 1. Effects of $mGlu_1$ receptor $+/+$ mice ($n = 7$) or $mGlu_1$ receptor $-/-$ ($n = 7$) on perforant path-dentate gyrus long-term potentiation. Consistent long-term potentiation was induced in $mGlu_1$ receptor $+/+$ animals (*A*). $mGlu_1$ receptor $-/-$ animals showed a reduced long-term potentiation of population spike amplitude (*B*). Top traces are representative e.p.s.ps taken from one experiment during the pre-tetanus period (1), immediately post-tetanus (2), and 1 h post-tetanus (3). Arrows show when the tetanus was induced (three trains 10 s apart, 400 Hz, eight impulses each). Each point is the average of three evoked potentials. Histograms show the mean and standard error ($n = 7$ for each group) of population spike recorded pre-tetanus (PRE), immediately post-tetanus (POST), and 1 h post-tetanus (1 h POST). Mutant mice differed from control at 1 h post-tetanus ($P < 0.05$, *t* test).

cal significance, however, between $mGlu_1$ receptor $-/-$ and $+/+$ mice in the response immediately post-tetanus (Fig. 1B). Mice lacking functional $mGlu_1$ receptors thus show less long-term potentiation in the dentate gyrus in vivo.

This result differs from our earlier study using the slice preparation (Conquet et al., 1994). The different result is unlikely to be due to the age of the mice, because similar ages (2–4 months) were used in both studies. A potential explanation is that the synaptic connectivity left intact in vivo might exert an inhibitory action within the hippocampus or between the hippocampus and other structures (e.g. cortex). The present result is consistent with the findings by Aiba et al. (1994) of a reduced long-term potentiation in CA1 cells. It would be interesting to test in vivo the $mGlu_1$ receptor-deficient mouse strain used by Aiba et al. (1994).

In conclusion, this study suggests an important role for mGlu receptors in synaptic plasticity. Because these mice are congenitally lacking $mGlu_1$ receptors, however, it is possible that these receptors are only required during development to establish a plastic state, and might not be needed for the expression of long-term potentiation per se.

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