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$G\alpha_q$-Deficient Mice Lack Metabotropic Glutamate Receptor-Dependent Long-Term Depression But Show Normal Long-Term Potentiation in the Hippocampal CA1 Region

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Long-term potentiation (LTP) and depression (LTD) are potential cellular mechanisms involved in learning and memory. Group I metabotropic glutamate receptors (mGluR), which are linked to heterotrimeric G-proteins of the G_q family (G_q and G_{11}), have been reported to facilitate both hippocampal LTP and LTD. To evaluate their functional role in synaptic plasticity, we studied LTD and LTP in the CA1 region of the hippocampus from wild-type, $G\alpha_q(-/-)$, and $G\alpha_{11}(-/-)$ mice. Basic parameters of the synaptic transmission were not altered in $G\alpha_q(-/-)$ and $G\alpha_{11}(-/-)$ mice. Moreover, these mice showed normal LTP in response to a strong tetanus and to a weak tetanus. However, LTD induced either by a group I mGluRs agonist or by paired-pulse low-frequency stimulation (PP-LFS) was absent in $G\alpha_q(-/-)$ mice. Moreover, PP-LFS caused potentiation of the synaptic transmission in these mice that was not affected by the NMDAR antagonist AP-5. These results show that G_q plays a crucial role in the mGluR-dependent LTD, whereas hippocampal LTP is not affected by the lack of a single member of the G_q family.

Key words: synaptic plasticity; hippocampus; metabotropic glutamate receptor; GTP-binding protein; gene targeting; mouse

Long-term potentiation (LTP) and long-term depression (LTD) represent potential cellular mechanisms of learning and memory (Bliss and Collingridge, 1993; Manahan-Vaughan and Braunwell, 1999). Both forms of synaptic plasticity depend critically on a rise in intracellular Ca^{2+} (Bear and Malenka, 1994; Zucker, 1999). In the CA1 region, the Ca^{2+} increase results largely from NMDAR-mediated influx (Morris et al., 1986; Dudek and Bear, 1992; McHugh et al., 1996). Metabotropic glutamate receptors (mGluRs) have emerged as another important element in synaptic plasticity (for review, see Bortolotto et al., 1999).

A role of mGluRs was first implied by the finding that receptor antagonists inhibit hippocampal LTP (Reymann and Matthies, 1989; Bashir et al., 1993a). In view of contradicting reports (Manzoni et al., 1994; Selig et al., 1995) (for review, see Bortolotto et al., 1999), Bortolotto et al. (1994) suggested that the stimulation of mGluRs activates intracellular signaling molecules supporting the induction of LTP until their activity is reversed. Fitting with this scheme, LTP is strengthened by prestimulating mGluRs (McGuiness et al., 1991; Otani et al., 1993). Remarkably, selective activation of group I receptors is sufficient to facilitate LTP in response to a weak tetanus (Cohen and Abraham, 1996; Cohen et al., 1998). The function of class I mGluRs in LTP is further emphasized by studies in mice lacking the $mGluR_5$ highly expressed in CA1 pyramidal cells (Lujan et al., 1996). $mGluR_5$-deficient mice show an impairment of LTP confined to the NMDA receptor component of synaptic transmission (Lu et al., 1997; Jia et al., 1998).

Similarly, LTD in the CA1 region is shown to exhibit a component depending on the function of mGluRs (Bashir et al., 1993b; Manahan-Vaughan, 1997; Oliet et al., 1997; Nicoll et al., 1998; Otani and Connor, 1998). Based on the effects of mGluR antagonists, Manahan-Vaughan (1997) suggested that LTD in the hippocampus requires synergistic activity of group I and II. Fitting with this idea, Overstreet et al. (1997) have reported that (±)-1-aminocyclopentane-*trans*-1,3-dicarboxylic acid, an agonist of group I and II mGluRs, induces LTD in the CA1 region. However, others have shown that mere stimulation of class I receptors is sufficient to generate LTD in various regions of the hippocampus (Palmer et al., 1997; Camodeca et al., 1999; Fitzjohn et al., 1999; Huber et al., 2000).

Thus, there is compelling evidence that group I mGluRs play a fundamental role in hippocampal synaptic plasticity. The group I receptors $mGluR_1$ and $mGluR_5$ couple to G-proteins of the G_q family, G_q and G_{11}, both expressed in hippocampal pyramidal cells (Mailleux et al., 1992; Milligan, 1993; Friberg et al., 1998; Tanaka et al., 2000). Like $mGluR_5$, G_q/G_{11} are primarily localized in the postsynaptic extrajunctional membrane (Tanaka et al., 2000). The function of these G-proteins in hippocampal synaptic plasticity remains elusive. To gain new insight, we analyzed LTP and LTD in mice lacking $G\alpha_q$ or $G\alpha_{11}$. Mutant mice exhibited normal LTP. However, mGluR-dependent LTD was absent in $G\alpha_q$ $(-/-)$ mice showing a critical role of G_q in this form of synaptic plasticity.

MATERIALS AND METHODS

Field EPSP recordings in hippocampal slices. Transverse hippocampal slices (400 μm thick) from wild-type, $G\alpha_q(-/-)$ and $G\alpha_{11}(-/-)$ mice were prepared, and field EPSPs (fEPSPs) in the CA1 region were recorded as described previously (Kleppisch et al., 1999). The stimulus intensity was adjusted to elicit ~40–50% of the maximal fEPSP ampli-

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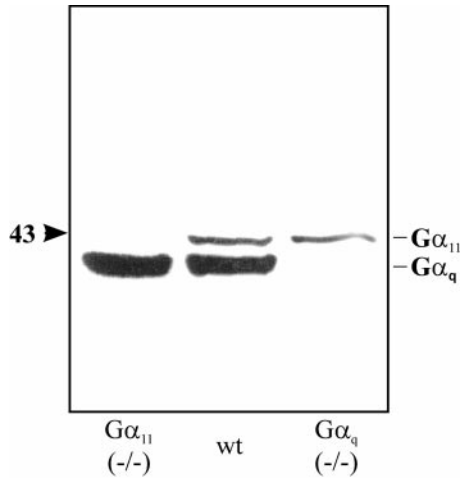

Figure 1. $G\alpha_q$ is the predominant form of the G_q family members expressed in the murine hippocampus. Immunoblots with hippocampal tissue using a common antibody against the C terminus of $G\alpha_q$ and $G\alpha_{11}$. Lanes were loaded with protein extracts from the hippocampus of wild-type (*central*), $G\alpha_{11}(-/-)$ (*left*), and $G\alpha_q(-/-)$ (*right*) mice, respectively.

tude. LTP was induced using either a relatively strong 100 Hz tetanus (3×30 pulses, 100 Hz, 5 sec pause between trains) or a weak theta burst (10×4 pulses with 100 Hz, 200 msec pause between bursts) in slices pretreated with the group I mGluR-selective agonist 3,5-dihydroxyphenylglycine (DHPG; 5 μM for 5 min) (Ito et al., 1992; Schoepp et al., 1994). LTD was induced either by application of DHPG (50 μM for 5 min) or by a paired-pulse low-frequency stimulation (600 or 900 pulse pairs with 1 or 3 Hz, interpulse interval 50 msec) adapted from a recently published protocol (Kemp and Bashir, 1997; Huber et al., 2000). The strength of synaptic transmission was assessed through the fEPSP slope. LTP and LTD were expressed as percentage of the fEPSP during the baseline recording. All data shown for the time course of the fEPSP slope are mean ± SEM. Statistical analysis was performed using the Student's *t* test for two independent means. *p* values of <0.05 were considered significant.

Animals. $G\alpha_q(-/-)$ and $G\alpha_{11}(-/-)$ mice originated from a cross between C57BL/6 mice and chimeras with a contributing 129/Sv background that were established by means of the conventional gene-targeting method (Offermanns et al., 1997a,b, 1998). The phenotype of $G\alpha_q(-/-)$ mice includes impaired motor coordination and defective platelet activation, whereas $G\alpha_{11}(-/-)$ mice have no overt dysfunction. Therefore, homozygous offspring from $G\alpha_q(+/-)$ mice and a $G\alpha_{11}$-deficient lineage was used in the present study. To minimize a possible impact of the undefined genetic background, we used littermates as control.

Immunoblotting. For Western analysis, hippocampal tissue samples were homogenized, and cholate extracts were separated on 10% SDS-polyacrylamide gel and blotted onto nitrocellulose membranes. The blots were probed with an $G\alpha_q/2fG\alpha_{11}$ antibody (Santa Cruz Biotechnology, Santa Cruz, CA) recognizing a common epitope at the C terminus of $G\alpha_q$ and $G\alpha_{11}$. Bound antibodies were detected using the ECL technique (Amersham Pharmacia Biotech, Arlington Heights, IL).

RESULTS

G_q is the predominant G-protein of the G_q family expressed in the murine hippocampus

G_q has been reported to represent the dominating subtype in the rat hippocampus (Milligan, 1993). The expression of the G_q family members G_q and G_{11} in the murine hippocampus was studied by immunoblotting tissue extracts from wild-type $G\alpha_{11}(-/-)$ and $G\alpha_q(-/-)$ mice with a common $G\alpha_q/G\alpha_{11}$ specific antibody. For the wild type, two bands were detected: one at 43 kDa corresponding to the $G\alpha_{11}$ subunit and a second more prominent corresponding to the $G\alpha_q$ subunit with a slightly lower apparent molecular weight than $G\alpha_{11}$ (Fig. 1, *central lane*). These data show that G_q is the principal form of the G_q family expressed in the murine hippocampus. The identity of the $G\alpha_{q/11}$ bands was confirmed using immunoblots of hippocampal extracts from $G\alpha_{11}(-/-)$ and $G\alpha_q(-/-)$ animals. These blots yielded only single bands corresponding to the remaining G-protein α-subunit (Fig. 1, *left* and *right lanes*). Remarkably, the concentration of $G\alpha_{11}$ was not altered in the hippocampus of $G\alpha_q(-/-)$ mice compared with the wild type.

Mice lacking $G\alpha_q$ or $G\alpha_{11}$ exhibit normal synaptic transmission in the CA1 region

$G\alpha_q(-/-)$ and $G\alpha_{11}(-/-)$ mice had no gross anatomical abnormalities in the brain, and the cellular layers in the hippocampus were regularly arranged (data not shown). To evaluate whether the gene deletions resulted in an universal defect of synaptic transmission, we examined the dependency of the fEPSP amplitude on the stimulus intensity (*I–O* relation) and the paired-pulse facilitation (PPF). The *I–O* relation in the two mutants, $G\alpha_q(-/-)$ and $G\alpha_{11}(-/-)$, was not significantly different from that observed in the wild type (Fig. 2*A*). The PPF represents a second important control parameter of the synaptic transmission, in particular of the presynaptic function. Mice lacking $G\alpha_{11}$ or $G\alpha_q$ exhibited normal PPF for interstimulus intervals ranging from 25 to 275 msec (Fig. 2*B*). Thus, the fundamental characteristics of the synaptic transmission were not altered in the mutant mice.

Mice lacking $G\alpha_{11}$ or $G\alpha_q$ show normal LTP in the hippocampal CA1 region

Mice lacking the $mGluR_5$ coupling to $G_{q/11}$ exhibit impaired LTP in the CA1 region (Lu et al., 1997; Jia et al., 1998). Initially, we studied the effect of $G\alpha_q$ or $G\alpha_{11}$ deficiency on LTP in the Schaffer collateral pathway using a relatively strong 100 Hz tetanus similar to that used in the study with $mGluR_5$-deficient mice. Under these conditions, LTP was not significantly altered in the $G\alpha_q(-/-)$ and in the $G\alpha_{11}(-/-)$ mice compared with the wild type (Fig. 3). The fEPSP slopes 1 hr after tetanus for the three genotypes were 134.8 ± 7.0% (wild type, $n = 8$ slices), 129.0 ± 8.4% ($G\alpha_q(-/-)$, $n = 9$ slices), and 139.5 ± 3.9% ($G\alpha_{11}(-/-)$, $n = 8$ slices) of the pretetanus control. Similarly, as described for group I mGluRs, the functional relevance of $G_{q/11}$ in LTP might depend on the tetanization strength (cf. Wilsch et al., 1998; Balschun et al., 1999). Therefore, we additionally tested a weak theta burst stimulation (10×4 pulses). Again, LTP induced with the theta burst was not different in the wild type (127.5 ± 6.5%; $n = 8$ slices), the $G\alpha_q(-/-)$ (125.2 ± 6.4%; $n = 8$ slices), and the $G\alpha_{11}(-/-)$ mice (126.3 ± 6.9%; $n = 9$ slices) (Fig. 4). Thus, mice lacking $G\alpha_q$ or $G\alpha_{11}$ do not show defective LTP in the CA1 region of the hippocampus.

mGluR-dependent LTD is absent in the hippocampal CA1 region of mice lacking $G\alpha_q$

The temporary inhibition of the fEPSP slope caused by DHPG was less pronounced in the $G\alpha_q(-/-)$ mice (data not shown), suggesting a possible functional role in depression of synaptic transmission. In view of the reports that selective group I mGluR agonists including DHPG induce LTD, the effect of DHPG on the fEPSP slope was studied in more detail. Therefore, a saturating concentration of DHPG (50 μM) was transiently applied (5 min) to the slices from matched wild-type, $G\alpha_q(-/-)$, and $G\alpha_{11}(-/-)$ mice (cf. Huber et al., 2000). As demonstrated in Figure 5*A*, DHPG induced LTD in the wild-type and $G\alpha_{11}(-/-)$ mice with no difference between the two genotypes. The fEPSPs

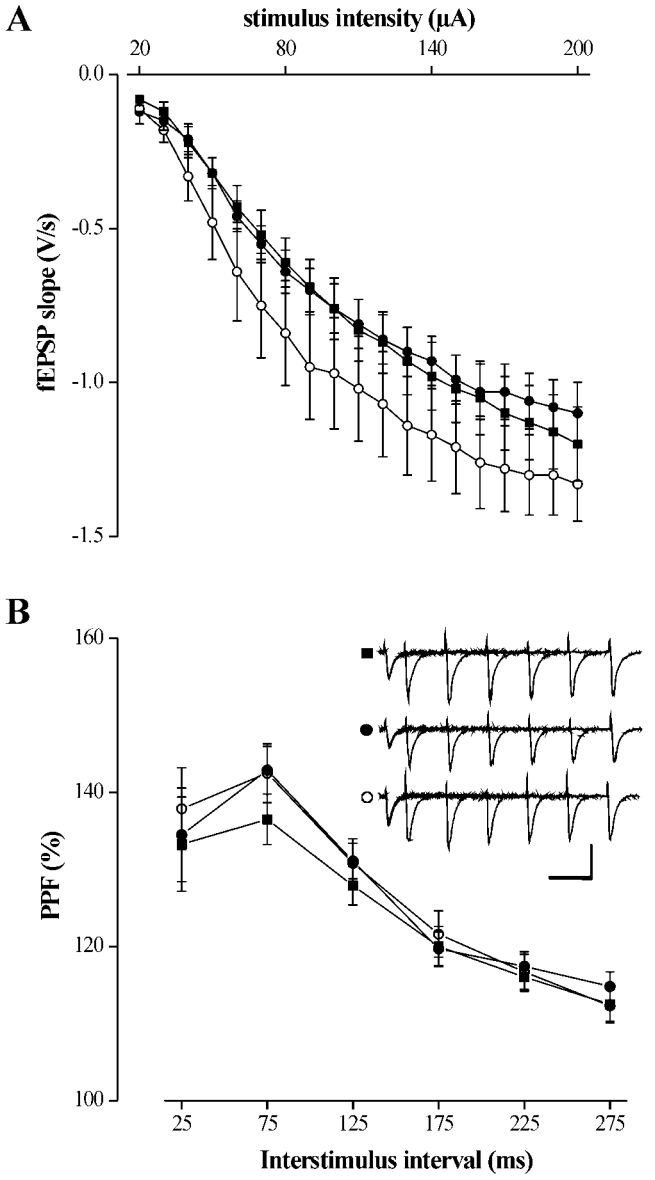

Figure 2. Mice deficient in $G\alpha_q$ and $G\alpha_{11}$ exhibit normal *I–O* relation and PPF. *A,* Shown is the relationship between the stimulation intensity (input) ranging from 20 to 200 μA and the corresponding fEPSP slope (output) for slices from wild-type (■; $n = 18$ slices), $G\alpha_q(-/-)$ (●; $n = 17$ slices), and $G\alpha_{11}(-/-)$ (○; $n = 15$ slices) animals. All points represent the mean ± SEM fEPSP in the corresponding genotype. *B,* PPF was studied for paired-pulse intervals in the range from 25–275 msec. Illustrated are the mean ± SEM of PPF as percentage for the wild type (■; $n = 14$ slices), $G\alpha_q(-/-)$ (●; $n = 13$ slices), and $G\alpha_{11}(-/-)$ (○; $n = 13$). The *inset* shows representative fEPSP recordings for the three genotype as indicated. Calibration: 50 msec, 0.5 mV.

slopes 50 min after treatment with DHPG amounted to 77.0 ± 4.4% (wild type, $n = 17$ slices) and 83.1 ± 3.9% ($G\alpha_{11}(-/-)$, $n = 16$ slices) of the control baseline ($p > 0.05$). In contrast to the $G\alpha_{11}(-/-)$ mice, $G\alpha_q$-deficient animals exhibited a complete loss of DHPG-induced LTD (Fig. 5*B*), although the initial transient inhibition of the synaptic transmission induced by DHPG was reduced only partially. The long-lasting depression of the synaptic transmission was reflected in the corresponding fEPSP slopes 50 min after wash-out of DHPG amounting to 72.5 ± 5.4% (wild type, $n = 18$ slices) and 101.3 ± 5.1% ($G\alpha_q(-/-)$, $n = 17$ slices)

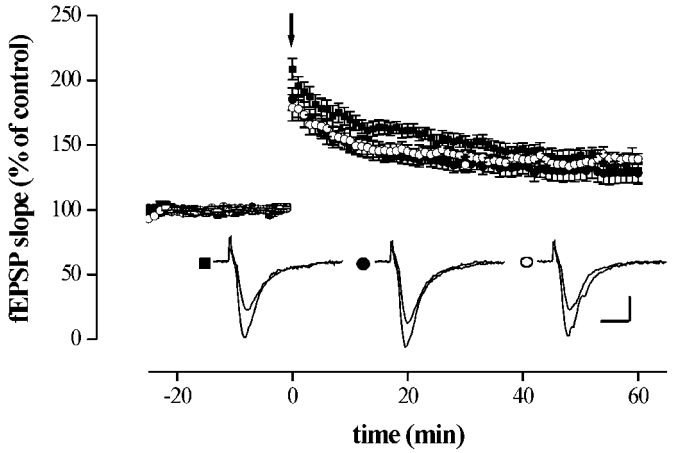

Figure 3. LTP induced by a strong tetanus is normal in $G\alpha_q(-/-)$ and $G\alpha_{11}(-/-)$ mice. Average potentiation of the fEPSP slope in slices from wild-type (■; $n = 7$ slices), $G\alpha_q(-/-)$ (●; $n = 9$ slices), and $G\alpha_{11}(-/-)$ (○; $n = 10$ slices) animals after a 100 Hz tetanus (3 × 30 pulses) indicated by the *arrow*. The fEPSP slope was normalized to the mean fEPSP slope during the baseline previous tetanization. Representative fEPSP recordings for the three genotypes are shown in the *inset*. Calibration: 0.5 mV, 10 msec.

of the baseline ($p < 0.01$). These findings clearly indicate a role of G_q for the LTD in the hippocampal CA1 region. To substantiate this notion, we examined synaptic plasticity after paired-pulse low-frequency stimulation (PP-LFS) (Fig. 6). Hippocampal slices from wild-type and $G\alpha_{11}(-/-)$ mice showed LTD in response to a 1 Hz PP-LFS. The fEPSP slopes 50 min after application were 88.9 ± 3.7% (wild type, $n = 8$ slices) and 89.9 ± 4.0% ($G\alpha_{11}(-/-)$, $n = 10$ slices) of the baseline in control ($p > 0.05$). Analogous to LTD induced by the group I mGluR agonist DHPG, LTD after 1 Hz PP-LFS was absent in hippocampal slices from $G\alpha_q(-/-)$ ($p < 0.05$). Moreover, the synaptic transmission in the $G\alpha_q(-/-)$ mice was potentiated (111.4 ± 5.6%; $n = 9$ slices). Two forms of activity-dependent LTD coexist in the hippocampus, a mGluR- and a NMDAR-mediated form. To

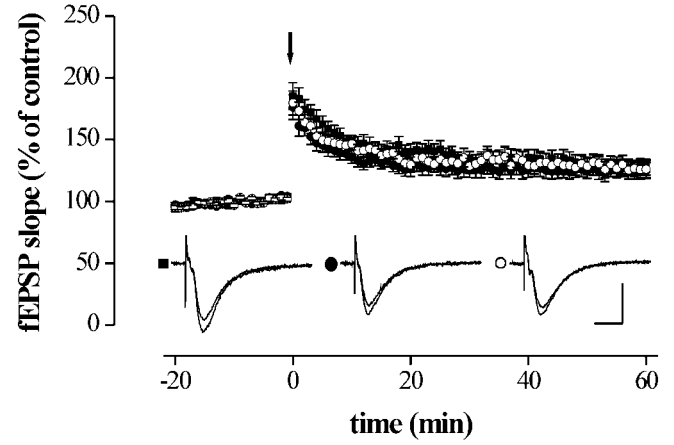

Figure 4. LTP induced by a weak theta burst is not altered in $G\alpha_q(-/-)$ and $G\alpha_{11}(-/-)$ mice. Average potentiation of the fEPSP slope after a weak theta burst (10 × 4 pulses) in slices from wild-type (■; $n = 8$), $G\alpha_q(-/-)$ (●; $n = 8$), and $G\alpha_{11}(-/-)$ (○; $n = 9$) animals. The fEPSP slope was normalized to the mean fEPSP slope during the baseline previous application of the theta burst indicated by the *arrow*. Representative fEPSP recordings for the three genotypes are shown in the *inset*. Calibration: 0.5 mV, 10 msec.

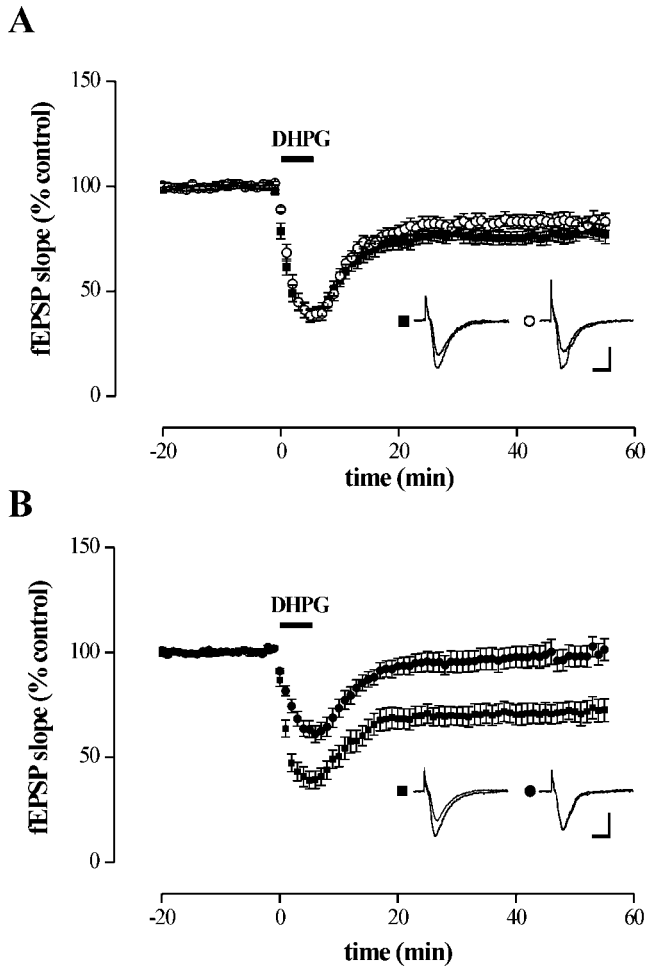

Figure 5. LTD induced by stimulation of mGluR group I is normal in slices from $G\alpha_{11}(-/-)$ mice but abolished in slices from $G\alpha_q(-/-)$ mice. Slices were treated with the mGluR group I agonist DHPG (50 μM) for 5 min to induce LTD. Shown is the time course of the fEPSP slope in slices from the wild-type (■; $n = 17$ slices) versus $G\alpha_{11}(-/-)$ (○; $n = 15$ slices) (*A*) and the wild-type (■; $n = 18$) versus $G\alpha_q(-/-)$ (●; $n = 17$) (*B*) animals, respectively. Representative fEPSP recordings for the genotypes as indicated are shown in the corresponding *insets*. Calibration: 10 msec, 0.5 mV.

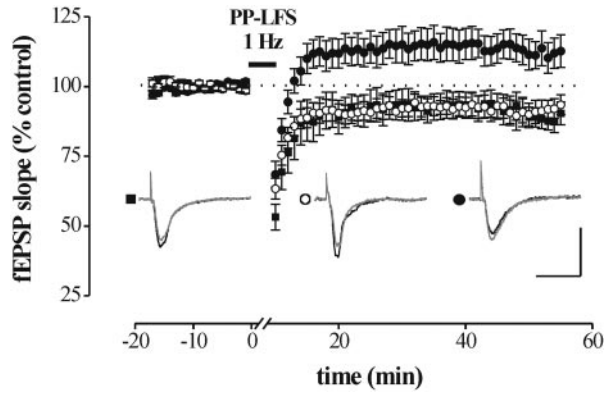

Figure 6. Low-frequency stimulation causes LTP instead of LTD in $G\alpha_q(-/-)$ mice. Shown is the time course of the average fEPSP slope after 600 pulse pairs at 1 Hz (PP-LFS) in slices from wild-type (■; $n = 8$ slices), $G\alpha_q(-/-)$ (●; $n = 9$ slices), and $G\alpha_{11}(-/-)$ (○; $n = 10$ slices) animals. Representative fEPSP recordings for the different genotypes in control (*black*) and 50 min after PP-LFS (*gray*) are shown in the *inset*. Calibration: 20 msec, 0.5 mV.

further differentiate between the role of G_q in these two forms, we blocked NMDARs with AP-5 (50 μM). The fEPSP slopes 40 min after the 1 Hz PP-LFS amounted to 87.9 ± 3.3% (wild type, $n = 12$ slices) and 118.7 ± 2.5% ($G\alpha_q(-/-)$, $n = 9$ slices) ($p < 0.05$) (Fig. 7) of the control baseline. Thus, under these conditions, hippocampal preparations from wild-type mice exhibited significant LTD in response to a 1 Hz PP-LFS, whereas the synaptic transmission in slices from $G\alpha_q(-/-)$ mice was again potentiated (Fig. 7).

DISCUSSION

Heptahelical mGluRs play an important role in synaptic plasticity (for review, see Bortolotto et al., 1999). For example, LTP and LTD in the hippocampus are facilitated by group I mGluRs (Palmer et al., 1997; Cohen et al., 1998; Fitzjohn et al., 1999; Camodeca et al., 1999; Huber et al., 2000). Individual elements in the signal transduction of these receptors supporting the long-term changes of synaptic transmission remain to be established. According to the general scheme, the effects of group I mGluR are mediated by G-proteins of the G_q family stimulating β-isoforms of phospholipase C (PLC). It has been reported recently that in the hippocampal CA3 region group I mGluRs can also signal independently of G-proteins (Heuss et al., 1999). Here, we studied the functional role of $G_{q/11}$ in hippocampal synaptic plasticity using the model of mice carrying a null mutation of the $G\alpha_q$ and $G\alpha_{11}$ gene, respectively. These mice had no overt morphological abnormalities of the brain and showed the normal arrangement of hippocampal cellular layers. In addition, basic parameters of the synaptic transmission (*I–O* relation and PPF) in the CA1 region were not altered.

Similar to expression data reported previously for the rat (Milligan, 1993), immunoblots demonstrated clearly that G_q is the predominant form of this family expressed in the murine hippocampus (Fig. 1). Expression of $G\alpha_{11}$ in the $G\alpha_q$-deficient mice was not altered compared with the wild type, arguing against a possible compensatory upregulation. A recent study also shows that within the mouse brain, Purkinje and hippocampal pyramidal cells display the maximum expression of $G\alpha_q$ mRNA (Tanaka et

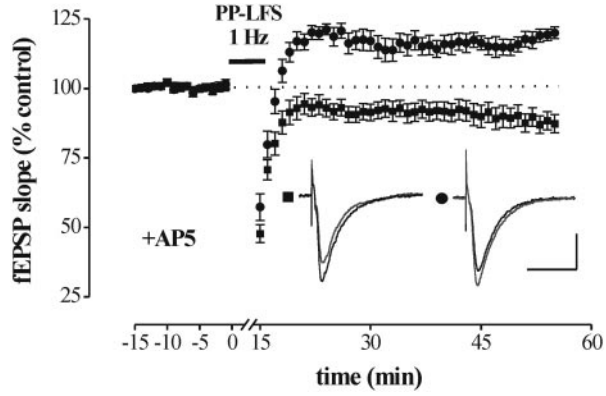

Figure 7. Altered synaptic plasticity of the $G\alpha_q(-/-)$ mice after low-frequency stimulation does not depend on NMDAR function. Shown is the time course of the average fEPSP slope after 900 pulse pairs at 1 Hz (PP-LFS) in slices from wild-type (■; $n = 12$ slices) and $G\alpha_q(-/-)$ (●; $n = 9$ slices) animals. AP-5 (50 μM) was present throughout all experiments. Representative fEPSP recordings in control (*black*) and 40 min after PP-LFS (*gray*) are shown in the *inset*. Calibration: 20 msec, 0.5 mV.

al., 2000). The two G-proteins G_q and G_{11} colocalize with the $mGluR_5$, the major subtype expressed in the CA1 region, at extrajunctional regions in pyramidal cell dendrites (Mailleux et al., 1992; Lujan et al., 1996; Tanaka et al., 2000), further supporting the view that perisynaptic stimulation of group I mGluR is mediated through these G-proteins.

Lu et al. (1997) reported that mice lacking the $mGluR_5$ exhibit reduced Schaffer collateral LTP after four trains of a 100 Hz stimulation that is confined to the NMDAR-dependent component. However, a 100 Hz tetanus induced equivalent LTP in the wild-type, $G\alpha_{11}(-/-)$, and $G\alpha_q(-/-)$ mice (Fig. 3). In the same way as reported for group I mGluRs (Wilsch et al., 1998; Balschun et al., 1999), the functional relevance of $G_{q/11}$ in LTP might be limited with the 100 Hz tetanus and become more prominent with weak tetanization. However, LTP induced with a weak theta burst stimulation (10×4 pulses) was also not altered in the $G\alpha_q(-/-)$ and $G\alpha_{11}(-/-)$ mice (Fig. 4). It has been reported that prestimulation of group I mGluRs facilitates LTP in the hippocampal CA1 region of the rat through a PLC-dependent mechanism (Cohen et al., 1998). However, pretreatment of mouse slices according to the protocol of Cohen et al. (1998) only slightly increased LTP (~15%) compared with the control. Again, no difference between the wild-type, $G\alpha_q$-, and $G\alpha_{11}$-deficient mice could be observed under these conditions (data not shown). Our data may suggest that LTP can be supported by both G_q and G_{11}. This could be tested rigorously in mice lacking the α-subunits of both G_q and G_{11}. Unfortunately, a double mutant generated by conventional gene targeting is not viable (Offermanns et al., 1998). Alternatively, we cannot exclude that group I mGluRs support LTP in a way independent of both G-proteins (cf. Heuss et al., 1999). Such a mechanism could underlie the specific defect of the NMDA receptor component of the fEPSP in $mGluR_5$-deficient mice (Lu et al., 1997).

In contrast to LTP, a significant part of LTD, which represents another important form of synaptic plasticity in the hippocampus, was found to be associated with the function of G_q. LTD in the CA1 region can be induced through direct stimulation of group I mGluRs (Palmer et al., 1997; Fitzjohn et al., 1999) and by LFS (Bear and Abraham, 1996; Kemp and Bashir, 1997; Huber et al., 2000). DHPG-induced LTD was completely eliminated in $G\alpha_q(-/-)$ mice but remained intact in $G\alpha_{11}(-/-)$ mice (Fig. 5). It is generally thought that the members of group I, mGluR1 and mGluR5, couple to both G_q and G_{11} without discriminating (Conn and Pin, 1997). However, our data show that these two G-proteins are not generally redundant in their synaptic function. Whereas both G_q and G_{11} might support a function of group I mGluRs in LTP, their function in LTD correlates with a signaling through G_q (but not through G_{11}). Interestingly, $G\alpha_q(-/-)$, but not $G\alpha_{11}(-/-)$ mice, exhibit defects in other regions of the CNS (Offermanns et al., 1997a). The mechanisms underlying this selectivity remain unclear. As recently shown, mGluR class I-dependent LTD in the CA1 region requires a rapid postsynaptic translation of pre-existing dendritic mRNA (Huber et al., 2000), which might suggest that G_q regulates the neuronal protein synthesis through a yet unknown mechanism.

LFS-induced LTD is more complex consisting of two mechanistically separate components inhibited by antagonists of NMDA and mGlu receptors, respectively (Dudek and Bear, 1992; Oliet et al., 1997; Nicoll et al., 1998). LFS-induced LTD in the $G\alpha_q(-/-)$ mice was, therefore, expected to be reduced just partially. Interestingly, a 1 Hz paired-pulse LFS, while generating significant LTD in the wild-type and the $G\alpha_{11}(-/-)$ mice, caused weak LTP in mice lacking $G\alpha_q$ (Fig. 6). Moreover, the NMDAR antagonist AP-5 had no effect on PP-LFS-induced LTD in the wild type, and $G\alpha_q(-/-)$ mice again showed LTP in response to 1 Hz paired-pulse LFS in the presence of AP-5 (Fig. 7). Therefore, changes in NMDAR function are obviously not involved in the conversion of LTD into slight LTP observed in mice lacking $G\alpha_q$. Altered synaptic plasticity in the $G\alpha_{11}(-/-)$ mice may result from unmasking alternative signaling mechanisms mediated neither by G_q-coupled receptors nor by NMDA receptors.

Besides the sustained depression, DHPG caused a pronounced short-term depression (STD) of the synaptic transmission that reversed rapidly after wash-out. It has been described recently that the selective mGluR antagonist LY 341495 eliminates LTD but does not block completely this transient inhibition induced by DHPG (Huber et al., 2000). Similar to this observation, STD, unlike LTD, was reduced only partially in the $G\alpha_q$ knock-out mice (Fig. 5). STD was not affected in the $G\alpha_{11}(-/-)$ animals. These results might reflect that LTD and STD depend on different signaling mechanisms or that the two G-proteins, G_q and G_{11}, can at least in part substitute each other functionally in STD. In summary, our data show that LTP in the CA1 region of the hippocampus is intact despite a deficiency of $G\alpha_q$ or $G\alpha_{11}$. However, the loss of $G\alpha_q$ abolished the mGluR-dependent component of LTD in the hippocampal CA1 region.

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