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The ATP-regulated K^+-channel inhibitor HMR-1372 affects synaptic plasticity in hippocampal slices

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Abstract

Long-term potentiation (LTP) and long-term depression of synaptic transmission in the hippocampus are widely studied models of learning and memory processes. The role of ATP-regulated K^+ channels (K^+_{ATP} channels), which are abundant in the brain, has not yet been studied in long-term potentiation or long-term depression. We investigated whether K^+_{ATP} channel inhibition by the highly selective K^+_{ATP}-channel blocker 1-[[5-[2-(5-*tert*-butyl-*o*-anisamido)ethyl]-2-methoxyphenyl]sulfonyl]-3-methylthiourea (HMR-1372), a novel putative class III antiarrhythmic, affects long-term potentiation or the long-term depression induced by 3,5-dihydroxyphenylglycine (30 μM) in submerged rat hippocampal slices. HMR-1372 (10 μM) did not affect basal synaptic transmission, paired pulse inhibition, long-term depression or long-term potentiation elicited by a weak (weak long-term potentiation) tetanus, but significantly amplified the long-term efficacy of long-term potentiation elicited by a strong tetanus (strong long-term potentiation). The K^+_{ATP}-channel inhibitor glibenclamide (20 μM) also ameliorated only strong long-term potentiation. Our data suggest that K^+_{ATP} channels are activated during or after induction of long-term potentiation and play a role in controlling synaptic excitability.

Keywords: Long-term potentiation; K^+_{ATP}-channel; Hippocampal slice, rat; HMR-1372; 3,5-Dihydroxyphenylglycine; Glibenclamide

1. Introduction

ATP-sensitive potassium (K^+_{ATP} channels) channels are widely expressed in many cell types including neurons (Ashcroft and Ashcroft, 1990; Liss and Roeper, 2001) and are inhibited by intracellular ATP (Quayle et al., 1997). During the past decade, it has become increasingly clear that K^+_{ATP} channels are involved in neuroprotection during ischemic episodes (Heurteaux et al., 1993; Takaba et al., 1997), but recent studies have indicated that these channels also affect learning and memory. K^+_{ATP}-channel openers have been found to induce amnesia and to impair spontaneous alternation performance in vivo, whereas inhibitors had an improving or no effect (Ghelardini et al., 1998; Stefani and Gold, 2001). Long-term potentiation (LTP) and long-term depression of synaptic transmission in the hippocampus are widely studied models of learning and memory processes. Although it was shown that K^+ channels in general play a role in long-term potentiation (Aniksztejn and Ben-Ari, 1991; Meiri et al., 1998; Kanterewicz et al., 2000) and long-term depression (Janigro et al., 1997) the way the various types of K^+ channels influence these plasticity phenomena is poorly understood and the role of K^+_{ATP} channels is virtually unknown.

In the hippocampus, ATP-regulated K^+ channels are predominantly found in interneurons and glia cells, but also in part of the pyramidal cells (Morre et al., 1989; Zawar et al., 1999; Brockhaus and Deitmer, 2000). The increased release of acetylcholine from striatal cholinergic interneurons and γ-aminobutyric acid (GABA) in substantia nigra

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slices during inhibition of these channels (Amoroso et al., 1990; Lee et al., 1997) indicates that there may be an influence on inhibitory transmission. As the functional importance of ATP-regulated K^+ channels for GABAergic interneurons and pyramidal cells is as yet unclear, we elucidated if the inhibition of ATP-regulated K^+ channels would cause an improvement or a deterioration of long-term potentiation.

Besides long-term potentiation, the long-term depression of synaptic transmission is another important plasticity phenomenon. The role of ATP-regulated K^+ channels has not as yet been examined in connection with long-term depression. Thus, it cannot be excluded that the activation of ATP-regulated K^+ channels contributes to this phenomenon by reducing neuronal excitability. In vitro, a chemically induced type of long-term depression can be easily elicited by an intense stimulation of group I metabotropic glutamate receptors (Schnabel et al., 1999; Huber et al., 2001). 3,5-Dihydroxyphenylglycine is the most specific known agonist for this type of receptor (Ito et al., 1992; Schoepp et al., 1994). In order to elucidate the role of K^+_{ATP} channels in synaptic plasticity, in this study we determined the effect of the novel, potent and specific K^+_{ATP}-channel blocker HMR-1372 (Kilbinger et al., 2002) and of the broad-spectrum K^+_{ATP}-channel blocker glibenclamide on different forms of plasticity. Since K^+_{ATP}-channel blockers are developed to treat noninsulin-dependent diabetes mellitus (Ligtenberg et al., 1995) and cardiac arrhythmias (Gögelein et al., 1999), it is important to know if and to what extent they can also alter processes involved in learning and memory formation.

2. Materials and methods

2.1. Hippocampal slice preparation

Seven to 8-week-old male Wistar rats (Tierzucht Schönwalde) were killed by a blow to the neck. After decapitation, the brain was quickly removed and placed into ice-cold artificial cerebrospinal fluid (ACSF) having the following composition (in mM): NaCl 124, KCl 4.9, $MgSO_4$ 1.3, $CaCl_2$ 2.5, KH_2PO_4 1.2, $NaHCO_3$ 25.6, D-glucose 10, saturated with 95% O_2, 5% CO_2, pH 7.4). Both hippocampi were isolated and transverse hippocampal slices (400-μm thickness) were prepared using a tissue chopper with a cooled stage. The slices were transferred into a submerged-type recording chamber where they were allowed to recover for at least 1 h before the experiment started. The chamber was constantly perfused with ACSF at a rate of 2.5 ml/min at 33±1 °C.

2.2. Field potential measurements

Synaptic responses were elicited by stimulation of the Schaffer collateral–commissural fibers in the *stratum radiatum* of the CA1 region using lacquer-coated stainless steel stimulating electrodes. Glass electrodes (filled with ACSF, 1–4 MΩ) were placed in the apical dendritic layer to record field excitatory postsynaptic potentials (fEPSPs). The initial slope of the fEPSP was used as a measure of this potential. The stimulus strength of the test pulses was adjusted to 30% of the of EPSP maximum. During baseline recording, three single stimuli (10 s interval) were averaged every 5 min. After tetanization, recordings were taken as indicated in the figures. Once a stable baseline had been established, long-term potentiation was induced by one of the following tetanization paradigms:

- weak tetanization—four times, two paired pulses were applied in intervals of 200 ms (weak tetanus). The interval between the paired pulses was 10 ms, the width of a single pulse 0.2 ms.
- strong tetanization—100 pulses at an interval of 10 ms and a width of the single pulses of 0.2 ms (strong tetanus) were applied three times at 10 min intervals.

Long-term depression was induced by application of 3,5-dihydroxyphenylglycine (Tocris Neuramin Bristol, UK), which was freshly dissolved in ACSF for each experiment and bath applied as indicated in Results.

Population spike responses were evoked by stimulation of the Schaffer collateral/commissural fibers and recorded in the stratum pyramidale of the CA1 region. Test stimuli were adjusted to elicit a population spike of about 40% of its maximum amplitude. The population spike amplitude was evaluated by calculating the voltage difference between the negative peak and the positive one preceding it. The basal synaptic transmission was recorded for at least 30 min before three paired pulses with interpulse intervals of 20, 40, 100, 200 or 500 ms were applied successively at an interval of one min per paired pulse. The interval between the different interpulse applications was also one min respectively. After another 60 min of basal synaptic transmission recording, HMR-1372 (10 μM) or ACSF was washed in for 30 min, and the paired pulse protocol was repeated in the presence of the inhibitor or ACSF.

The novel highly selective K^+_{ATP}-channel blocker 11-[[5-[2-(5-*tert*-butyl-*o*-anisamido)ethyl]-2-methoxyphenyl]sulfonyl]-3-methylthiourea (HMR-1372, Aventis Pharma Deutschland, Frankfurt am Main, Germany) was freshly dissolved in ACSF and glibenclamide (Tocris Neuramin) was freshly dissolved in dimethyl sulfoxide (DMSO) for each experiment and bath-applied as indicated in Results. The protocols used in this study were approved by the institutional ethics committee.

2.3. Statistics

All values are given as mean±S.E.M. As indicated in Results, the Mann–Whitney *U*-test or the analysis of

variance (ANOVA) with repeated measures was used to compare the field potentials between two groups of differentially treated slices (i.e., control vs. drug treatment) where appropriate.

3. Results

In the hippocampus, K^+_{ATP} channels are predominantly found in interneurons. Thus, if they open during activation of the interneuron, the resulting hyperpolarization should reduce GABA release and may therefore affect GABA-dependent processes such as the paired pulse inhibition of the population spike. In order to test this hypothesis, we applied paired pulses in the presence and absence of HMR-1372 at 20, 40, 100, 200 and 500 ms intervals and monitored their effects on the population spike amplitude. The resulting ratios of the amplitudes elicited between the second population spike and the first population spike [ACSF vs. HMR-1372 (10 μM)] were at 20 ms: 0.48±0.11 vs. 0.47±0.13, at 40 ms: 0.78±0.15 vs. 0.81±0.15, at 100 ms: 0.94±0.10 vs. 0.94±0.10, at 200 ms: 0.81±0.07 vs. 0.85±0.07 and at 500 ms: 1.14±0.04 vs. 1.15±0.04, respectively (n=8, not significant, Mann–Whitney U-test). As can be expected when GABAergic inhibition is present, we observed a clear inhibition of the second population spike at the 20-ms interval. Paired pulse inhibition was also observed at the 40-ms interval and at the 500-ms interval there was a slight paired pulse facilitation. HMR-1372 (10 μM) did not alter the paired pulse responses at any of the intervals tested, indicating that HMR-1372 does not affect GABAergic or a delayed type of inhibition.

Since K^+_{ATP}-channel open probability may increase with strength or duration of the stimulus we applied a weak tetanization paradigm consisting of repetitive paired pulse stimuli (four times two paired pulses in intervals of 200 ms) and monitored the effect of HMR-1372 (10 μM) on synaptic efficacy indicated by the slopes of the fEPSPs. Under control conditions, this paradigm elicits a weak long-term potentiation (Wilsch et al., 1998) that lasts for at least 2 h (Fig 1A). HMR-1372 (10 μM) caused a slight but insignificant increase

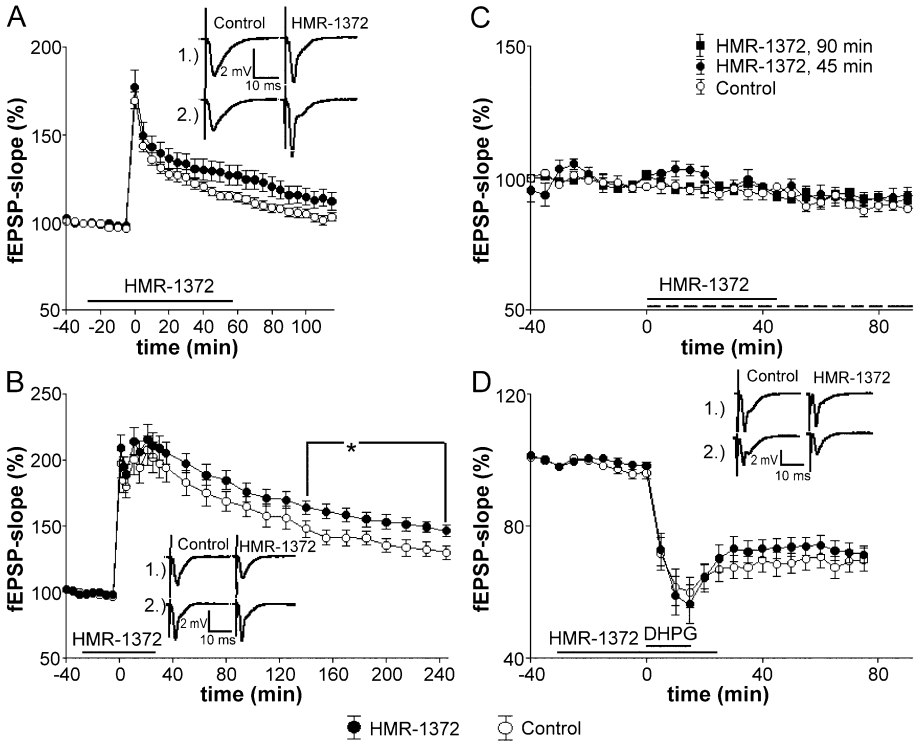

Fig. 1. Effect of HMR-1372 (10 μM) on long-term potentiation and 3,5-dihydroxyphenylglycine (DHPG)-induced long-term depression. HMR-1372 (10 μM) affected the maintenance of (A) long-term potentiation elicited by a weak tetanus only marginally (Control: n=10; HMR-1372: n=11) but significantly ameliorated the maintenance of (B) long-term potentiation induced by a strong tetanization (Control: n=11; HMR-1372: n=11; *P<0.05; ANOVA with repeated measures). The potentiation persisted for at least 120 and 240 min, respectively. The stimuli were applied at time point 0. Horizontal bars indicate the time of drug application. (C) HMR-1372 (10 μM) did not affect baseline recordings (Control: n=4) when applied for 45 min and washed out thereafter (HMR-1372, full bar, n=4) or when permanently present for 90 min (HMR-1372, broken bar, n=4). (D) HMR-1372 (10 μM) did not alter the 3,5-dihydroxyphenylglycine (DHPG, 30 μM) induced long-term depression (Control: n=10; HMR-1372: n=11). Analogue traces represent typical recordings of single experiments taken 10 min before tetanization (1), and 100 min after tetanization (2) in panel A; 10 min before tetanization (1), and 240 min after tetanization (2) in panel B and 10 min before (1), and 100 min after 3,5-dihydroxyphenylglycine application (2) in panel D.

of the long-term potentiation (Fig. 1A). Application of the strong tetanization paradigm (three times 100 pulses at 10 min intervals) resulted in a long-term potentiation that lasted for at least 6 h under control conditions (Fig. 1B). When HMR-1372 (10 μM) was present, there was a moderate improvement of long-term potentiation that became significant about 2 h after induction (Fig. 1B). Since this effect might have been due to a slow-onset potentiation caused by the prolonged utilization or the washout of the compound, we monitored the baseline effects of HMR-1372 (10 μM) when present for 90 min and when washed out after 45 min (Fig. 1C). The compound did not affect the baseline under these circumstances.

It has been shown that 3,5-dihydroxyphenylglycine induces a metabotropic glutamate receptor-dependent long-term depression in hippocampal area CA1. The underlying mechanisms, however, are as yet not fully understood. It has not been investigated whether or not the mechanisms involved particularly in the initial phase of the response may lead to a decrease in synaptic ATP levels. In that case, K^+_{ATP} channels would open and thus contribute to the phenomenon. As expected 3,5-dihydroxyphenylglycine (30 μM) induced a pronounced depression of synaptic transmission that partially recovered during washout of the compound (Fig. 1D). HMR-1372 (10 μM) affected neither initiation nor maintenance of 3,5-dihydroxyphenylglycine-induced long-term depression.

In order to compare the effects of the rather cardiac specific compound HMR-1372 with a more general inhibition of K^+_{ATP} channels, we reexamined the long-term potentiation experiments using the broad-spectrum inhibitor glibenclamide (20 μM). Unlike HMR-1372 glibenclamide ameliorated all phases of the strong long-term potentiation, but did not affect the weak long-term potentiation at all (Fig. 2).

4. Discussion

In this study, we demonstrated that K^+_{ATP}-channel inhibition can induce a lasting increase in long-term potentiation, which indicates that K^+_{ATP} channels are active not only during ischemic episodes but also under nonpathological conditions. In the light of the observation that K^+_{ATP} channels predominantly occur in interneurons in area CA1 (Zawar et al., 1999), our results are somewhat surprising. In theory, one would expect that if there is a decline in synaptic ATP content and an increased K^+_{ATP}-channel opening during or after tetanization, this would mainly concern the interneurons, resulting in a hyperpolarization and a diminished GABA release. Channel inhibition would reverse the effect and would thus lead to no alteration of or even a decrease in long-term potentiation. This mechanism is not excluded by our data. When HMR-1372 or glibenclamide is present during tetanization such an effect may be masked by K^+_{ATP}-channel inhibition in the pyramidal cells, leading to an increase in excitability and to a net improvement of long-term potentiation.

Our finding that inhibition of K^+_{ATP} channels by HMR-1372 or glibenclamide during tetanization amplifies long-term potentiation does not necessarily indicate that the stimuli significantly lowered the neuronal ATP content in general. It can be sufficiently explained by a brief local decline in ATP due to the re-establishment of the ion gradients by ATP consuming transporters such as Na^+/K^+-ATPase or Ca^{2+}-ATPase at the synapses activated. HMR-1372 and glibenclamide had no effect during baseline, as can be expected when ATP levels are high and K^+_{ATP} channels therefore closed. Few repetitive stimuli, as applied during baseline and in the paired pulse protocol, are insufficient to activate them. More pronounced stimulation

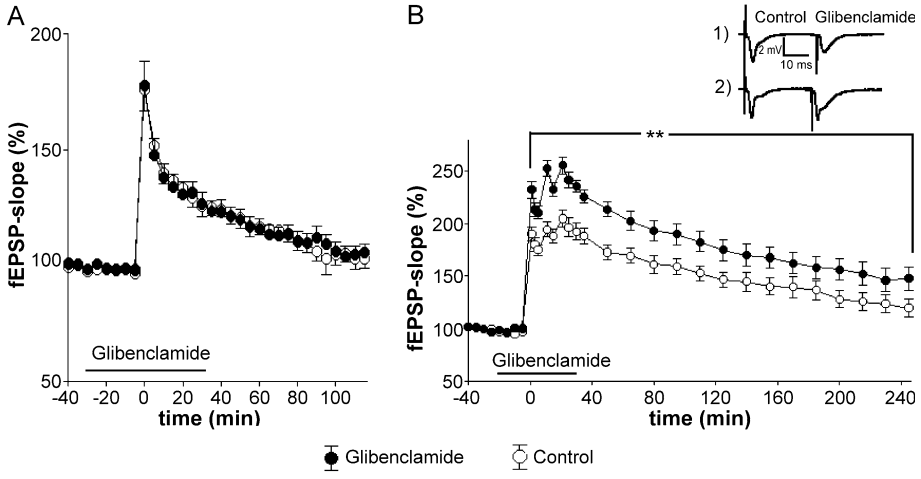

Fig. 2. Effect of glibenclamide on long-term potentiation. (A) Glibenclamide (20 μM) did not alter long-term potentiation elicited by a weak tetanus (Control: n=8; Glibenclamide: n=8). In contrast, glibenclamide (20 μM) significantly ameliorated the (B) long-term potentiation induced by a strong tetanization (Control: n=9; Glibenclamide: n=11; $^{**}P<0.01$; ANOVA with repeated measures). The potentiation persisted for at least 120 and 240 min, respectively. The stimuli were applied at time point 0. Horizontal bars indicate the time of drug application. Analogue traces represent typical recordings of single experiments taken 10 min before tetanization (1) and 240 min after tetanization (2).

as in the tetanization protocols, however, appears to lower ATP levels to an extent that causes the channels to open. It is therefore likely that one of the natural functions of K^+_{ATP} channels may be the damping of synaptic excitability. Inhibition of these channels by HMR-1372 during tetanization apparently increases stimulus efficacy to an extent that results in an improved long-term potentiation, which may in turn positively affect memory. Consistent with this assumption, glibenclamide has been found to enhance spontaneous alternation performance (Stefani and Gold, 2001) and K^+_{ATP}-channel openers to impair passive avoidance memory (Ghelardini et al., 1998).

Because only strong long-term potentiation was ameliorated by the inhibitors, our data suggest that only a strong tetanization causes a decline in the synaptic ATP content sufficient to alter plasticity. Accordingly, simple paired pulse responses, 3,5-dihydroxyphenylglycine-induced long-term depression, and weak long-term potentiation were not at all or at best mildly affected. It cannot be ruled out though, that the lack of effect of HMR-1372 on 3,5-dihydroxyphenylglycine-induced long-term depression is due to a direct inhibition of K^+_{ATP} channels by the G_α subunit of the group 1 metabotropic glutamate receptor, as has been observed in inspiratory brainstem neurons (Mironov and Richter, 2000).

It is as yet unclear if the K^+_{ATP} channels act pre- or postsynaptically or both, because neurons might contain different subtypes (Cui et al., 2001) and information about the subcellular distribution of these channels is lacking. Our data are in line with findings that K^+_{ATP}-channel opening reduces transmitter release (Amoroso et al., 1990; Lee et al., 1997; Kilbinger et al., 2002). In that case, presynaptic hyperpolarisation would limit Ca^{2+} entry through voltage-gated channels. Alternatively, postsynaptic hyperpolarisation may affect the Mg^{2+} block of *N*-methyl-D-aspartate receptors and thus limit postsynaptic Ca^{2+} entry. Both mechanisms would lead to a diminution in long-term potentiation and can be overcome by a K^+_{ATP}-channel inhibitor. We have shown that K^+_{ATP}-channel inhibition by HMR-1372 only affected the maintenance phase, whereas the broad-spectrum inhibitor glibenclamide ameliorated all phases of the strong long-term potentiation. These results might indicate that HMR-1372, in contrast to glibenclamide, only inhibits a subset of the K^+_{ATP} channels activated during LTP induction. It is conceivable that HMR-1372 preferentially inhibits pre- or postsynaptic K^+_{ATP} channels, while glibenclamide inhibits both. An involvement of mitochondrial K^+_{ATP} channel inhibition by glibenclamide that might have affected synaptic ATP content can also not be excluded.

In conclusion, our data indicate that K^+_{ATP} channels modulate long term potentiation induction by attenuating synaptic excitability. Together with previous findings correlating memory and K^+_{ATP} channels this makes them promising candidates for fine tuning the weights of synapses in memory processes.

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