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Preferential block of desensitizing AMPA receptor in hippocampal neurons by γ-D-glutamylaminomethylsulfonic acid

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Abstract

The (*RS*)-α-Amino-3-hydroxy-5-methyl-4-isoxazolopropionic acid (AMPA)/kainate receptor-channel complex mediates fast components of excitatory synaptic currents in the central nervous system. Distinguishing between these components is a difficult pharmacological task. As was recently reported, γ-D-glutamylaminomethylsulfonic acid (GAMS) may be a selective kainate receptor antagonist. We have tested this possibility in experiments which were carried out on acutely isolated rat hippocampal neurons. It appeared that 1 mM GAMS first blocked 83 ± 1% of the fast desensitizing 128 μM AMPA-gated current, but only 38 ± 6% of the non-desensitizing current component and reached, at higher GAMS concentrations, a plateau at about 50% of the control steady state current level. In contrast to the blocking action of GAMS on AMPA-gated currents, 4-fold higher concentrations of GAMS were needed to block currents elicited by 256 μM kainate application. It is suggested that several subunit compositions of the AMPA-gated receptor could coexist on a single hippocampal cell. Furthermore, GAMS has a certain preference for subunit assemblies which could mediate fast desensitizing and, a portion of, the non-desensitizing current component.

Keywords: AMPA/kainate receptor; Desensitizing current, fast; GAMS (γ-D-glutamylaminomethylsulfonic acid); 6-Cyano-7-nitroquinoxaline-2,3-dione; Hippocampal neuron, rat

1. Introduction

The most common excitatory neurotransmitter in the brain is glutamate (Glu) which acts on two types of Glu receptors namely ionotropic (ionotropic Glu receptors) (Monaghan et al., 1989) and metabotropic receptors (metabotropic Glu receptors, Tanabe et al., 1992). At present the ionotropic Glu receptors can be divided into three subtypes according to their preference for pharmacological tools (Seeburg, 1993). The first shows a preference for *N*-methyl-D-aspartic acid (NMDA) and is thus described as the NMDA receptor, which has a marked Ca^{2+} permeability (Hume et al., 1991). Due to its Ca^{2+} permeability it is widely accepted that the NMDA subtype is important for the induction of long-term potentiation (Collingridge et al., 1983). Additionally, NMDA receptor malfunction is involved in many pathological states in the brain (Choi and Rothman, 1990). The second ionotropic Glu receptor subtype displays a marked preference for (*RS*)-α-amino-3-hydroxy-5-methyl-4-isoxazolopropionic acid (AMPA) (Keinänen et al., 1990) and the third for kainic acid (kainate) (Hollmann et al., 1989). The AMPA receptor-channel complex is thought to be responsible for mediating mainly fast electrophysiological events (Tang et al., 1989). The major ion carrier of the current which AMPA and kainate gate is Na^+ (McDonald and Nowak, 1990).

Currently, a daunting pharmacological problem exists, in that there are no specific antagonists to distinguish between non-NMDA ionotropic Glu receptor subtypes. Without such pharmacological tools, until now it has proven impossible to establish the physiological role of each of the non-NMDA ionotropic Glu receptors. This is further complicated by the fact that non-NMDA ionotropic Glu receptors can be assembled from different subunit combinations (for example: AMPA receptor: Glu_1 receptor to Glu_4 receptor

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(Keinänen et al., 1990); kainate receptor: Glu_5 receptor to Glu_7 receptor and $kainate_1$ and $kainate_2$ (Werner et al., 1991; Bettler et al., 1992)). Each of these subunits determines the specific characteristics of AMPA or kainate receptor channels (Lomelli et al., 1994; Jonas et al., 1994). Uneven expression of these subunits creates a number of possibilities for AMPA/kainate-gated channel regulation (Lambolez et al., 1992; Bochet et al., 1994). Different subunit expression patterns have been observed during development of the brain (Bahn et al., 1994; Monyer et al., 1991). Such an important characteristic as Ca^{2+} selectivity is determined by Glu_2 receptors (for review see Gasic and Heinemann, 1991; Sommer and Seeburg, 1992) and it has been demonstrated recently that age-related Ca^{2+} selectivity is mediated via this subunit (Pagliusi et al., 1994). However, little is known as yet about precise subunit composition and mechanisms of regulation in naturally occurring systems, except that different combinations really exist (Ozawa and Lino, 1993). One more example of molecular diversity of ionotropic Glu receptors is that AMPA receptors have low-and high-affinity AMPA binding sites (Vodyanoy et al., 1993).

Nevertheless, it has been demonstrated recently that a well known non-specific Glu receptor antagonist, γ-D-glutamylaminomethylsulfonic acid (GAMS), can selectively discriminate between AMPA-gated and kainate-gated currents in *Xenopus* oocytes (Zhou et al., 1993). This offers hope that GAMS may also distinguish between AMPA-and kainate-gated ionotropic Glu receptors in rat hippocampal CA1 neurons. The aim of the present study was to test such a possibility.

Recent investigation of the blocking effect of the AMPA/kainate receptor antagonist, 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(*F*)quinoxaline (NBQX), has demonstrated that this substance influences fast- and non-desensitizing AMPA-gated currents in a different manner (Parsons et al., 1994). At low NBQX concentrations the non-desensitizing current component was facilitated, while the fast desensitizing AMPA-gated current was markedly reduced. We have tested whether GAMS can display a similar preference.

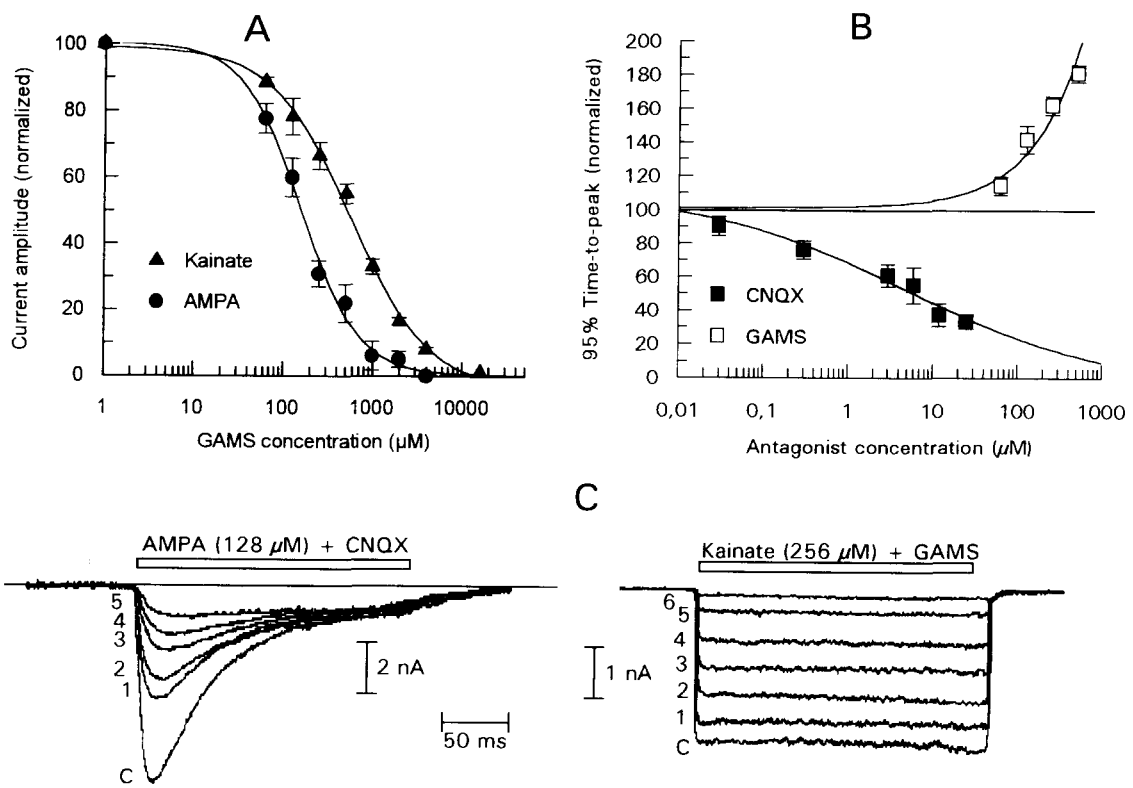

Fig. 1. The blocking action of GAMS on AMPA- and kainate-gated currents. A: Dose-response curves for GAMS blocking action on 128 μM AMPA- and 256 μM kainate-gated currents. Solid lines represent data fit by 4-parameter logistic equation. GAMS blocked both AMPA- and kainate-gated currents with a 3.6-fold higher potency for the AMPA-gated current. Corresponding IC_{50} values were 157 ± 16 μM (mean ± S.E.M.; $n = 10$) for AMPA-gated and 566 ± 60 μM for kainate-gated current ($n = 8$). Hill coefficients were 1.3 ± 0.2 and 0.99 ± 0.09 respectively. Time-to-peak values (TTP) for 128 μM AMPA-gated currents, which were normalized to the value displayed by the control trace at zero concentration of antagonist, are in B (upper curve), showing a prolongation with increasing GAMS concentration. For comparison, this was in contrast with the CNQX blocking action (lower curve), where such values decreased in parallel with the elevation of CNQX concentration. Sample traces for GAMS blocking action are presented in C, where increasing GAMS concentrations for the blocking of AMPA-gated (left) and kainate-gated currents (right) are marked with numerals, where 'c' is control; 1: 64 μM; 2: 128 μM; 3: 256 μM; 4: 512 μM; 5: 1024 μM; 6: 2048 μM.

The findings of this study argue in favor of the possibility that GAMS is not a selective kainate receptor antagonist, but rather a preferential blocker of the fast desensitizing AMPA-gated current component, displaying no facilitation of the non-desensitizing current component. A specific AMPA-preferring subunit combination can be a target for such a preferential inhibition by GAMS.

2. Materials and methods

Experiments were carried out on hippocampal CA1 neurons which were acutely dissociated from brain slices of 18-day-old Wistar rats, as was described previously (Wilsch et al., 1994). The ionic composition of the extracellular solution was: NaCl 155 mM; Hepes 10 mM; $CaCl_2$ 2 mM; pH 7.2. Pyramidal cells were inves-

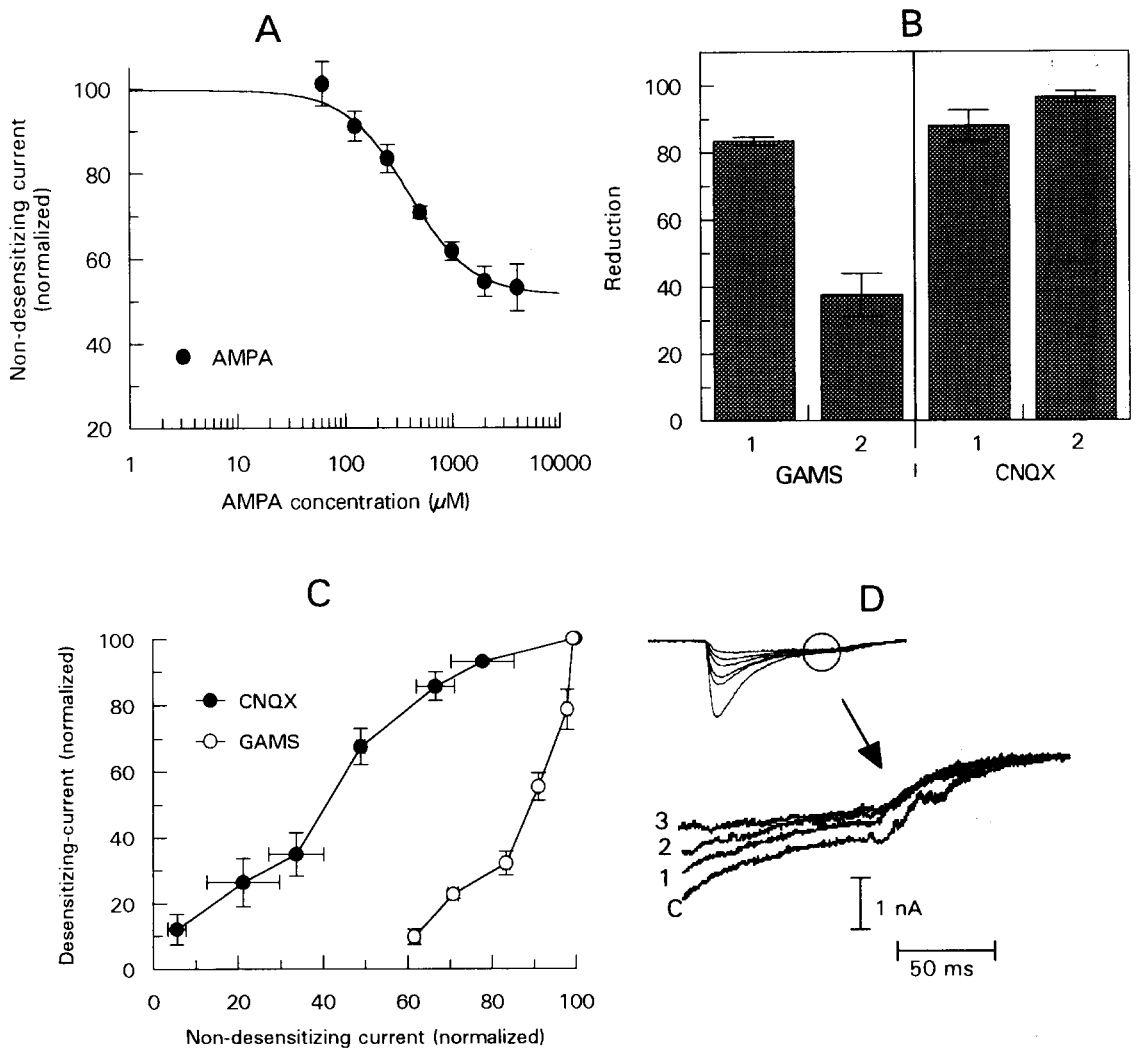

Fig. 2. Preferential block of the fast desensitizing AMPA-gated current by GAMS. Data points for making the dose-response curve were measured 120 ms (three desensitization time constants) after the 128 μM AMPA-gated current peaked. GAMS blocked a fraction of the non-desensitizing current component, approaching a plateau at about 50% of the control steady state current level. The fast desensitizing AMPA-gated current was already absent at GAMS concentrations exceeding 1 mM (see also Fig. 1A). Such a difference for 1 mM GAMS concentration is shown in B (left columns; $n = 10$) in more detail. At this concentration, the fast desensitizing component was reduced by 83 ± 1% (1) while the non-desensitizing component was reduced only by 38 ± 6% (2). The more potent AMPA/kainate receptor antagonist, CNQX, did not display such a preferential block (right columns; $n = 5$). At a concentration of 25 μM CNQX, the fast desensitizing component was reduced by 88 ± 5% (1) with the non-desensitizing component being reduced by 96 ± 2% (2). The ratios of desensitizing and non-desensitizing current components blocked by CNQX and GAMS (full concentration range) are shown in C. The upper-right point is a control, followed (from left to right) by data points for the following GAMS concentrations (μM): 1024; 512; 256; 128; 64 and for CNQX concentrations (μM): 24; 12; 6; 3; 0.3; 0.03. CNQX tended to block fast and non-desensitizing current components in the same manner (unity slope), while GAMS blocked the fast desensitizing component more efficiently. Steady state current traces for selected GAMS concentrations are presented on an expanded scale in D, where 'c' is a control trace; 1: 256 μM; 2: 512 μM; 3: 1024 μM.

tigated using a whole-cell patch-clamp/concentration-jump technique. The patching process was performed according to standard procedures (Hamill et al., 1981). Patch pipettes were pulled from Clark glass capillaries (GCI 50 TF-10) and filled with intracellular solution. The ionic composition of the latter was: CsF 120 mM. Pipette resistances were about 1.5 MΩ. All experiments were performed at 22°C and at −100 mV holding potential. The current traces displayed were digitally filtered at 0.5 kHz.

Fast pulse application of chemicals (concentration jump) was done with a technique described previously (Pidoplichko and Reymann, 1994). In the present experiments a 200-ms-or 2-s-long concentration pulse was usually applied. The average time of solution exchange over the cell with 13 pF membrane capacitance was complete in about 12 ms. Flow velocity in our setup (65 μm/ms) was close to 100 μm/ms, as reported for precise patch experiments (Colqohoun et al., 1992).

Chemicals from Tocris Neuramin: (*RS*)-α-amino-3-hydroxy-5-methyl-4-isoxazolopropionic acid (AMPA), kainic acid (kainate), 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) and γ-D-glutamylaminomethylsulfonic acid (GAMS) were diluted in corresponding solvents and then in extracellular solution to yield the desired concentrations.

3. Results

When applied at concentrations higher than 4 mM, GAMS blocked both fast and non-desensitizing

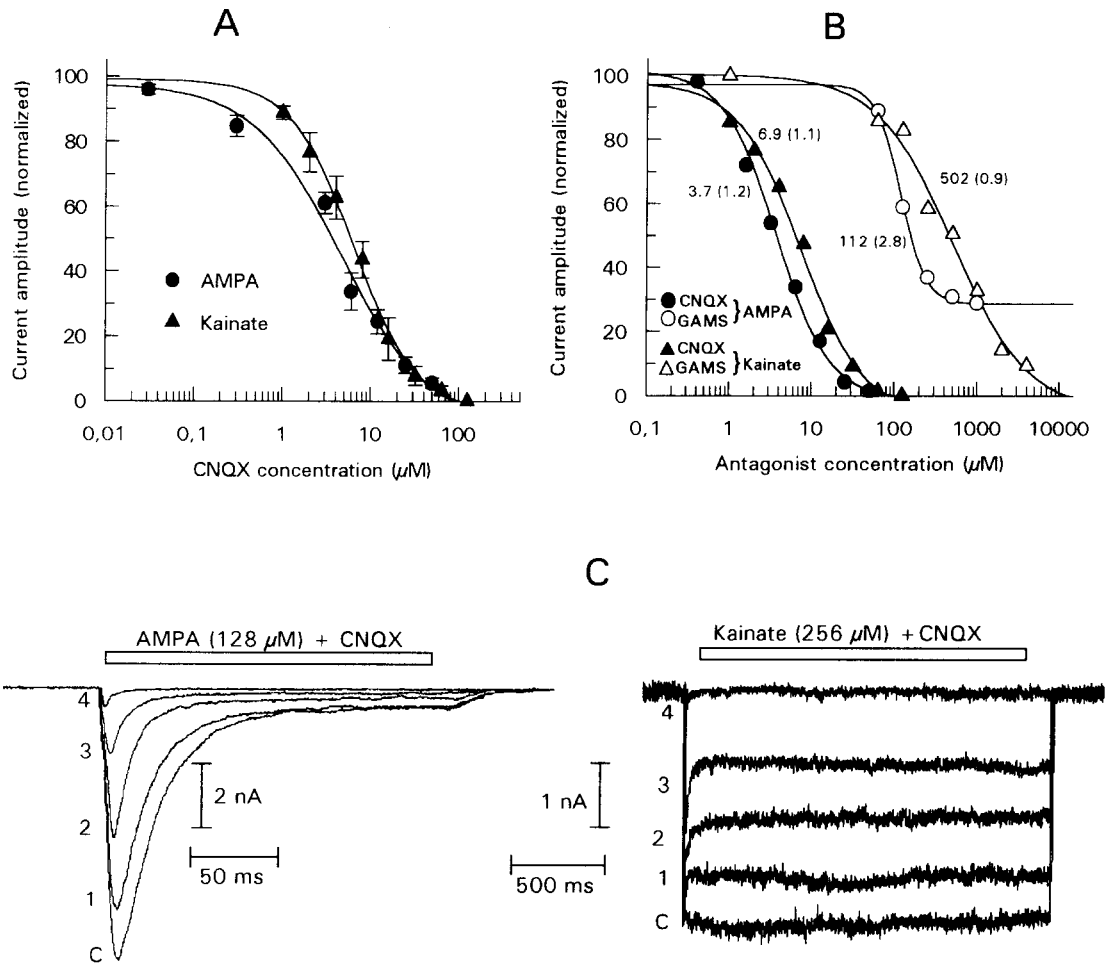

Fig. 3. CNQX blocking action on 128 μM AMPA- and 256 μM kainate-gated currents. CNQX, being much more potent than GAMS, blocked both AMPA- and kainate-gated currents. Dose-response curves, presented in A, approximated data points with $IC_{50} = 4.1 \pm 0.7$ μM for 128 μM AMPA-gated currents ($n = 5$) and with $IC_{50} = 6.3 \pm 0.5$ μM for 256 μM kainate-gated currents ($n = 7$). Hill coefficients were 1.0 ± 0.2 and 1.2 ± 0.1 correspondingly. The CNQX-blocking action on AMPA-gated currents was similar to that for kainate-gated ones. Direct comparison of the CNQX and GAMS blocking action is shown in B for selected cells. IC_{50} (in μM) and Hill coefficient (in brackets) values are shown near the corresponding curves. The dose-response curve for CNQX blocking action on kainate-gated currents was only shifted to the left as compared with the one for GAMS (due to lower potency of the latter substance). Selected AMPA- (left) and kainate-gated (right) current traces, reflecting CNQX blocking action, are presented in C. Numerals near current traces indicate concentrations (in μM) 1: 3; 2: 6; 3: 12; 4: 24. The reduction of time-to-peak values can be clearly seen in the example demonstrating AMPA-gated currents (see also Fig. 1B).

AMPA-gated and kainate-gated whole-cell inward currents in our preparation. AMPA and kainate were used in concentrations which were close to the corresponding EC_{50} values (Jonas and Sakmann, 1992). However, dose-response relationships for the GAMS blocking action on AMPA/kainate receptor-gated currents demonstrated a marked preference of this substance for the fast desensitizing AMPA-gated current. The apparent dissociation constant (IC_{50}) for the inhibition of fast 128 μM AMPA-gated currents (measured at the peak of the response) was 157 ± 16 μM ($n = 10$) and was 3.6 times higher (566 ± 60 μM; $n = 8$) for 256 μM kainate-gated non-desensitizing currents (Fig. 1A). The Hill coefficient for the inhibition by GAMS of the fast desensitizing AMPA-sensitive Glu receptor subtype was estimated as 1.3 ± 0.2, and for the non-desensitizing kainate-sensitive subtype as 0.99 ± 0.09. This suggests a one-to-one receptor-antagonist binding interaction with the latter. GAMS blocked fast AMPA-gated components. The time-to-peak values of the AMPA-gated current increases, in contrast to those with CNQX, due to increasing GAMS concentrations (i.e. in parallel with the decrease of the current amplitude, Fig. 1B and C (traces at left)). At concentrations higher than 2 mM the non-desensitizing kainate-gated current was completely blocked by GAMS (Fig. 1A, see also C (traces at right)).

Interestingly, this substance failed to induce complete block of a non-desensitizing component of 128 μM AMPA-gated currents in all of the neurons tested. The dose-response curve for inhibition by GAMS of non-desensitizing AMPA-gated currents demonstrated saturation of the blocking action (Fig. 2A). Such a GAMS-resistant current component was observed even at higher GAMS concentrations (up to 4 mM). At this concentration the reduction of the non-desensitizing current component was in the range of $50 \pm 10\%$ while the fast desensitizing component was totally blocked (Fig. 2B, see also traces in Fig. 1C and Fig. 2D).

In order to study the differences in the antagonist action of GAMS and CNQX (a non-selective AMPA/kainate antagonist (Honore et al., 1988)) at ionotropic Glu receptors in hippocampal neurons, the blocking action of CNQX on AMPA-and kainate-gated currents was tested (Fig. 3A). CNQX blocked 128 μM AMPA-gated and 256 μM kainate-gated currents with IC_{50} values of 4.1 ± 0.7 μM ($n = 5$) and 6.3 ± 0.5 μM ($n = 7$) respectively. The Hill coefficient for the CNQX-induced AMPA-gated current block was 1.0 ± 0.2, and for the kainate-gated current 1.2 ± 0.1.

The dose-response curve for the CNQX blocking action on AMPA-and kainate-gated currents, which was recorded on selected CA1 cells, is presented in Fig. 3B. The dose-response relationship for the blocking action of GAMS on AMPA-gated currents (measured at the peak of the desensitizing current and as a combination of desensitizing and non-desensitizing components) is also presented in Fig. 3B. The Hill coefficient of the curve was 2.8 with the IC_{50} value of 112 μM. This curve displays a GAMS-resistant steady state component, which further illustrates the previously mentioned apparent GAMS selectivity for a fraction of a non-desensitizing AMPA-gated currents (Fig. 2A).

The blocking action of CNQX on AMPA- and kainate-gated currents (Fig. 3A and B, and example traces in Fig. 3C) confirms that CNQX does not distinguish well between AMPA-and kainate-gated currents, or between fast and non-desensitizing AMPA-gated current components. The shortening of time-to-peak values was consistent with the 'flickering AMPA-gated channel block' induced by CNQX (Fig. 3C). The difference in the mechanisms of the antagonistic action of GAMS and CNQX on AMPA-gated currents, as reflected by activation kinetics, is illustrated in Fig. 1B.

4. Discussion

It is known that GAMS is a non-specific non-NMDA receptor antagonist (Davies and Watkins, 1985). Due to the high concentrations required by this substance to produce an antagonistic effect, pharmacological research was shifted to a different class of AMPA/kainate receptor antagonists, namely quinoxalinediones (Honore et al., 1988).

In the recent investigation by Zhou et al. (1993), evidence that GAMS selectively blocked kainate-gated currents in *Xenopus* oocytes, which express ionotropic Glu receptor subtypes from the chick brain, was presented. We then set about to examine this effect in the rat central nervous system. We therefore checked the possibility of the existence of such a discriminatory effect in hippocampal rat CA1 neurons. It was not possible to demonstrate a selective block of kainate-gated currents by GAMS in our preparation, which is in line with the observations for other competitive AMPA/kainate receptor antagonists (Yamada et al., 1989). Such observations are supported by the evidence that the response to exogenously applied AMPA and kainate is mediated via a common receptor (Patneau and Mayer, 1991). Our results thus differed from the conclusions of Zhou et al. (1993), but perhaps can be explained by the following factors.

The first factor could be the expression pattern of Glu receptor subunits which may be different from that native in our preparation.

It is also possible that fast GAMS-sensitive desensitizing AMPA receptors with a very low relative weight were expressed in *Xenopus* oocytes. Thus the currents gated by them were masked by the dominating non-desensitizing GAMS-resistant component.

Another possible factor is that inferior time resolution is an intrinsic feature of conventional bath application of substances in whole oocyte experiments. The outcome of this would be that fast desensitizing AMPA-gated currents would not be resolved. Thus the results of Zhou et al. (1993) could be related mainly to the non-desensitizing AMPA-and kainate-gated current components.

At present it is hard to select between the factors mentioned above.

Though GAMS failed to distinguish selectively between AMPA-and kainate-gated currents in our preparation, it showed an interesting feature. GAMS induced a block of AMPA-gated current components in a manner different from that recently demonstrated for NBQX (Parsons et al., 1994). NBQX displayed its blocking action on the fast-desensitizing AMPA-gated current, at the same time facilitating the non-desensitizing current component. Increasing concentrations of NBQX finally led to a total block of both current components. In contrast, GAMS displayed no facilitating effect on the non-desensitizing current component and even with higher GAMS concentrations 50% of the non-desensitizing current component was unaffected by GAMS.

A preferential block of the fast AMPA-gated current component could be due to higher selectivity of GAMS for a certain subunit composition of the AMPA receptor-channel complex, which is naturally expressed in acutely isolated CA1 neurons of immature rats, and which mediates such a current. It is possible to draw a parallel with the fact that two different (high and low) affinity states of the AMPA-gated receptor channel exist, which can be converted into each other (Hall et al., 1992). Such a conversion may take place during some plasticity phenomena. Switching between high- and low- affinity states was also discussed in conjunction with the possible NBQX mechanism of action (Parsons et al., 1994). Concerning our observations of the apparently GAMS-resistant component of non-desensitizing AMPA-gated current, it is suggested that AMPA receptors, gating such a component in hippocampal neurons, are similar to those GAMS-resistant ones, expressed in *Xenopus* oocytes in the Zhou et al. (1993) experiments.

It is concluded that the important problem of finding a Glu receptor antagonist which selectively distinguishes between AMPA- and kainate-preferring subtypes still remains unsolved. GAMS displays a blocking action on both the above-mentioned ionotropic Glu receptor subtypes. However, due to its ability to distinguish weakly (about a 4-fold difference in the IC_{50} values) between fast desensitizing AMPA-gated and non-desensitizing kainate-gated current components, GAMS may prove a tool for more detailed investigations of AMPA/kainate receptors, thus reviving an interest in this substance as a backbone for designing new ionotropic Glu receptor antagonists.

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