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Effect of AMPA receptor modulators on hippocampal and cortical function

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Abstract

Attention has focused on drugs that modulate AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid) receptors because of their potential for enhancing memory and treating certain pathologies that involve glutamatergic neurotransmission. The aim of this study was to compare and contrast the functionality of positive allosteric modulators of AMPA receptors in the hippocampus and medial prefrontal cortex. Electrically stimulated EPSPs (excitatory postsynaptic potential) in the hippocampus were augmented by CX516 [(1-quinoxaline-6-ylcarbonyl)piperidine], aniracetam and 1-BCP [(1-(1,3-benzodioxol-5-ylcarbonyl)piperidine] and not by cyclothiazide. Using grease gap electrophysiology, it was found that the mode of application dramatically altered the effect of the modulators of AMPA-induced depolarization. When added simultaneously with AMPA, aniracetam, 1-BCP and CX516 augmented the response in the frontal cortex. However, in the hippocampus, only aniracetam and cyclothiazide augmented the response when simultaneously added to AMPA. Therefore, in addition to regional variations, there appears to be differences in modulator response dependent upon whether a response is generated endogenously or exogenously by AMPA.

Keywords: AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid); AMPA receptor modulator; Cortex; Hippocampus

1. Introduction

Glutamate receptors can be split into ionotropic (NMDA/AMPA and kainate) or metabotropic subtypes. Of the ionotropic receptors, AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid) receptors mediate most of the fast excitatory amino acid transmission in the central nervous system (CNS). AMPA receptors are cation-selective pentameric hetero-oligomers formed by combinations of the subunits GluR1, GluR2, GluR3 and GluR4 (Hollmann et al., 1989; Boulter et al., 1990; Keinanen et al., 1990; Sommer and Seeburg, 1992; Wisden and Seeburg, 1993; Fletcher and Lodge, 1996). Each subunit can be expressed as a flip or flop isoform via RNA editing (Sommer et al., 1990; Lomeli, et al., 1994). Expression is regulated regionally (Boulter et al., 1990; Keinanen et al., 1990; Sommer et al., 1990; Wisden and Seeburg, 1993; Fletcher and Lodge, 1996) and developmentally (Monyer et al., 1991). Hippocampal dentate granule, CA1 and CA3 cells express GluR1, GluR2 and GluR3; only CA1 cells express GluR D also. Cerebellar granule cells express only GluR2 and GluR4, Bergmann glia GluR1 and GluR4; and spinal cord motoneurons have GluR1 GluR2, GluR3, GluR4 (Wisden and Seeburg, 1993; Fletcher and Lodge, 1996). Broadly speaking, the abundance of GluR1 and GluR2 subunits is high in projection glutamatergic neurons, while interneurons (often GABAergic) express less GluR2 and more GluR4 (Geiger et al., 1995). In addition, the expression of flip and flop variants of the above subunits is heterogeneous. Projection neurons preferentially express flip variants (however, hippocampal CA1 pyramidal cells express predominantly flop variants) while interneurons predominantly express flop variants (Wisden and Seeburg, 1993; Geiger et al., 1995). Therefore, a large amount of heterogeneity of AMPA receptors is seen across the CNS.

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The distribution of the various AMPA subunits would not be so crucial if they did not convey a difference in function. In this regard, the abundance of GluR2 conveys a positive correlation with desensitization time of AMPA receptors, while GluR4 conveys the opposite effect (Geiger et al., 1995). Therefore, the rise and fall time of AMPA responses across the CNS depends upon the subunit composition. Calcium permeability is also correlated with subunit composition. Studies have shown that recombinant AMPA receptors lacking GluR2 subunits have a high Ca^{2+} permeability, while recombinant receptors expressing GluR2 show a low permeability (Hume et al., 1991; Burnashev et al., 1992). This has obvious implications for calcium influx related phenomena such as long lasting changes in synaptic strength (Malenka, 1991; Teyler et al., 1994) and neurotoxicity (Choi, 1988). Together, the published data indicates that AMPA responses may vary markedly in different regions of the CNS. This, in turn, would also be true for drugs that directly modulate AMPA responses.

Attention has focused on drugs that modulate AMPA receptors because of their potential for enhancing memory and treating certain pathologies. Strengthening excitatory synapses may compensate for loss of or decrease in synaptic strength associated with aging or brain disease, and lead to greater perceptual, motor and cognitive performance. Positive allosteric modulators of AMPA may have an advantage over direct acting agonists or compounds that promote glutamate release, in that such drugs could increase glutamatergic tone, without the obvious liability for direct receptor-mediated excitotoxicity. Aniracetam, CX516, 1-BCP, IDRA-21 and cyclothiazide are valuable research tools for investigating positive allosteric modulation of AMPA receptors and may indeed prove useful in the clinic for such disease states as Alzheimer's disease or schizophrenia (Lee and Benfield, 1994; Lynch et al., 1996, 1997; Bigge and Nikam, 1997; Ingvar et al., 1997; Vanover, 1997). There is evidence that AMPA subunit composition effects the affinity of AMPA receptor agonists and antagonists (Stein et al., 1992) and the effects of modulators (Johansen et al., 1995; Hennegriff et al., 1997; Kessler et al., 1998). The aim of this study was to compare and contrast the functionality of these positive allosteric modulators of AMPA receptors in the hippocampus and medial prefrontal cortex.

2. Materials and methods

2.1. Animals

Male, Sprague–Dawley rats (125–175 g) were maintained and housed according to the standards set by the Investigational Animal Care and Use Committee at Hoechst Marion Roussel, Bridgewater, NJ, USA. Rats had access to food and water ad libitum with a 12-h light/dark cycle.

2.2. Hippocampal slice preparation for electrically stimulated EPSP recording

Methodology performed as per Schilp et al. (1999). Rats were sacrificed, the brain dissected out and the hippocampus was removed from the right hemisphere. Transverse slices (400 μm) were cut on a tissue chopper (Stoelting, USA) from the middle section of the hippocampus and placed in ice cold, oxygenated (95% O_2/5% CO_2) artificial cerebral spinal fluid (ACSF) containing (mM): NaCl 125.0, $NaHCO_3$ 25.0, KCl 1.9, KH_2PO_4 1.3, $MgSO_4$ 2.0, $CaCl_2$ 2.0, glucose 11.0 (pH 7.3–7.4). Slices were then transferred to a tissue bath with a gravity-fed ACSF flow rate of approximately 4 ml/min. The bath temperature was held at 28°C for 30 min, then raised to 34°C for the remainder of the experiment.

At least 60 min after slice preparation, a glass microelectrode (2–4 MΩ) filled with 2 M NaCl was inserted into the stratum radiatum region of the CA1. Evoked EPSPs (extracellular postsynaptic potentials) were generated by stimulating the Schaffer collateral bundle with a twisted bipolar stimulating electrode (Nichrome Formvar, A–M Systems, USA). Stimulus pulses of 0.1-ms duration were applied once per 30 s under the control of software (Spike2, CED, UK) via an isolated stimulator (Digitimer, model #DS2A). Signal amplification was performed using a Cyberamp 320 (Axon, USA) and digitized with a CED micro1401 A–D converter (CED, UK). Waveform analysis and response amplitudes were analyzed using Spike2 software (CED, UK). After a stable recording period of approximately 30 min, the slices were subjected increasing concentrations of drugs and their effect on baseline noted.

2.3. Preparation of cortex and hippocampus for grease gap recording

Rats were sacrificed and the brain was rapidly removed. Hippocampal slices were prepared as above except for the angle of cut: this was performed as described by Martin et al. (1989). For the preparation of cortical slices, the frontal half of the brain was placed in chilled oxygenated (95% O_2/5% CO_2) ACSF containing (mM): NaCl 118.0, $NaHCO_3$ 25.0, KCl 2.1, KH_2PO_4 1.2, $MgSO_4$ 2.0, $CaCl_2$ 2.0, glucose 11.0 (pH 7.3–7.4). 500 μM coronal slices (Bregma +1.7–3.2 mm) were taken with the aid of a vibratome (Vibratome series 1000, Technical Products International, USA). The slices were then placed in room temperature oxygenated ACSF for a further 30 min. Subsequently, the slices were hemisected with a razor blade and a wedge of tissue formed such that the dorsal cortical surface was approximately 1.5-mm wide and the ventral surface formed a point (Harrison and Simmonds, 1985). Wedges were taken from slices containing the prefrontal cortex (Fig. 1).

Cortical and hippocampal wedges were the placed in a two-compartment bath and a greased (high vacuum sili-

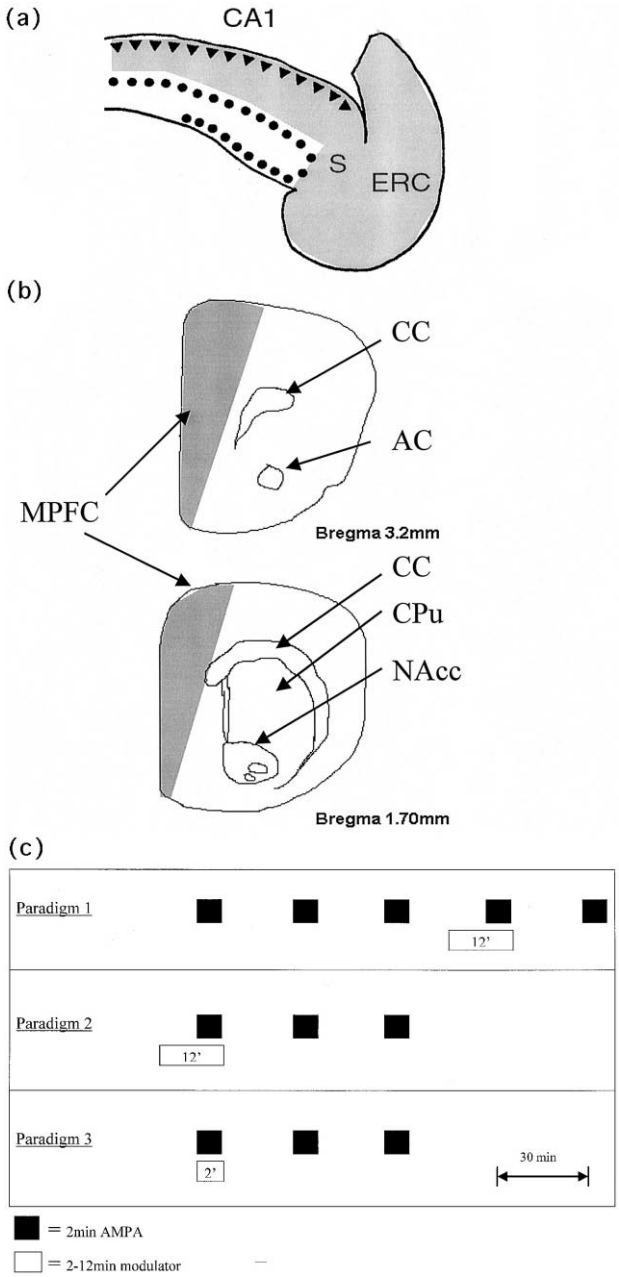

Fig. 1. Schematic representations of hippocampal (Panel a) and cortical sections (Panel b) used in this grease gap assays. Shaded areas indicate paring of the slices with which the recording were made. Abbreviations: CA1 — CA1 area of hippocampus, S — subiculum, ERC — entorhinal cortex, CC — corpus callosum, AC — anterior commisure, MPFC — medial prefrontal cortex, CPu — caudate putamen, NAcc — nucleus accumben. (c) Schematic representations of methodology used in Paradigms 1, 2 and 3. Each AMPA presentation was for 2 min separated by 30 min. The duration and time point of the modulators were varied.

cone grease, BDH, UK) barrier placed such that a high-resistance seal was formed between the two compartments (Harrison and Simmonds, 1985). Oxygenated ACSF was perfused through the two compartments separately at 2 ml/min for at least 1 h. The DC potential between the two compartments was monitored via Ag/AgCl electrodes. The signal was amplified by a headstage (AI405, Axon, USA) and fed into a high-impedance amplifier (Cyberamp 380, Axon, USA). The analogue signal was converted to a digital signal (micro1401, CED, UK) and analyzed with the aid of computer software (Spike2, CED). Drugs were added to one compartment only. Three experimental paradigms (Paradigms 1, 2 and 3) for applications of drugs were used in the current study and these are described graphically in Fig. 1b. All paradigms were carried out at room temperature.

2.4. Materials

Aniracetam and CX516 [(1-quinoxaline-6-ylcarbonyl) piperidine] were synthesized by Hoechst Marion Roussel. 1-BCP [(1-(1,3-benzodioxol-5-ylcarbonyl)piperidine], cyclothiazide, IDRA-21 [7-chloro-3-methyl-3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxide), CNQX (6-cyano-7-nitroquinoxaline-2,3-dione) and AMPA were purchased from RBI, USA.

3. Results

3.1. Electrically stimulated EPSP recording from hippocampal slices

Fig. 2 illustrates the potentiation of electrically stimulated EPSP amplitude in area CA1 of the hippocampus. The low potency of all the compounds makes determination of maxima difficult. In addition, solubility of compounds was a problem as DMSO (dimethyl sulfoxide) was never allowed to exceed 0.5%. Also, we noted the high variability in the response of the EPSP to the modulators; for a given concentration, the response (increase in EPSP height) could be between 10% and 140%. In line with

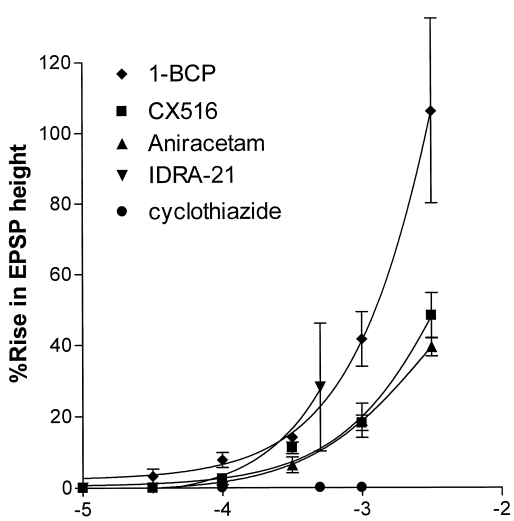

Fig. 2. Concentration–response relationship of modulators in electrically stimulated EPSP height. $N = 4–6$.

previously reported data, cyclothiazide did not elicit an increased EPSP amplitude. Aniracetam, CX516, 1-BCP and IDRA-21 caused significant increases in EPSP height above baseline at the highest concentrations used (*t*-test, $P < 0.05\%$).

3.2. Grease gap studies using hippocampal and cortical wedges

Concentration–response curves were generated in the hippocampus and cortex to exogenously applied AMPA (Fig. 3). The EC_{50} values were 8.5 μM [1.2–59.6 μM, 95% CL] in the cortex and 15.5 μM [3.0–79.3 μM, 95% CL] in the hippocampus. A dose of 10 μM was chosen as the test dose as this was approximately the EC_{50} value in both structures.

In the wedge studies following Paradigm 1, a stable baseline to exogenously applied AMPA was achieved. The fourth AMPA application was then accompanied with a 10-min pre-exposure of a modulator. Unexpectedly, none of the modulators effected the amplitude of the AMPA response at concentrations up to 1 mM (Fig. 4a). The presence of CNQX (10 μM), applied in the same manner, caused a substantial reduction in hippocampal and cortical responses.

In an effort to forego any effect of pre-exposures of AMPA on the modulator response, the modulators were applied before the first AMPA application. This approach unveiled a potentiation of the response to cortical AMPA by 1-BCP only (Fig. 4b). Again, CNQX had an antagonist effect in this preparation.

Modulators of AMPA have been shown to interact with the AMPA receptor recognition site and displace or augment ligand binding (Kessler et al., 1998). The AMPA receptor is prone to desensitization (Wisden and Seeburg, 1993; Fletcher and Lodge, 1996). Thus, it was hypothesized that pre-exposure of a modulator may effect its functional effect. Co-application of modulator with AMPA (with no pre-exposure) elicited positive modulatory effects

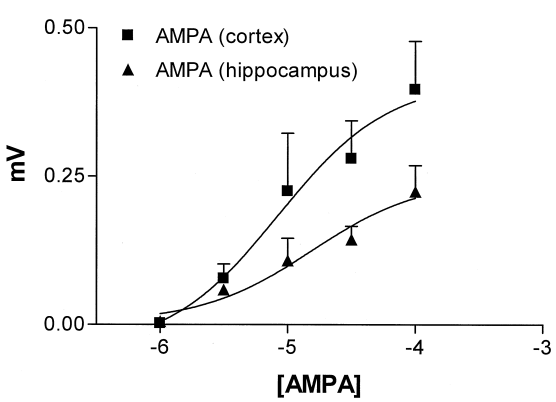

Fig. 3. Concentration–response relationship of AMPA-induced depolarization in hippocampal and cortical slices in the grease gap assay. $N = 6–8$.

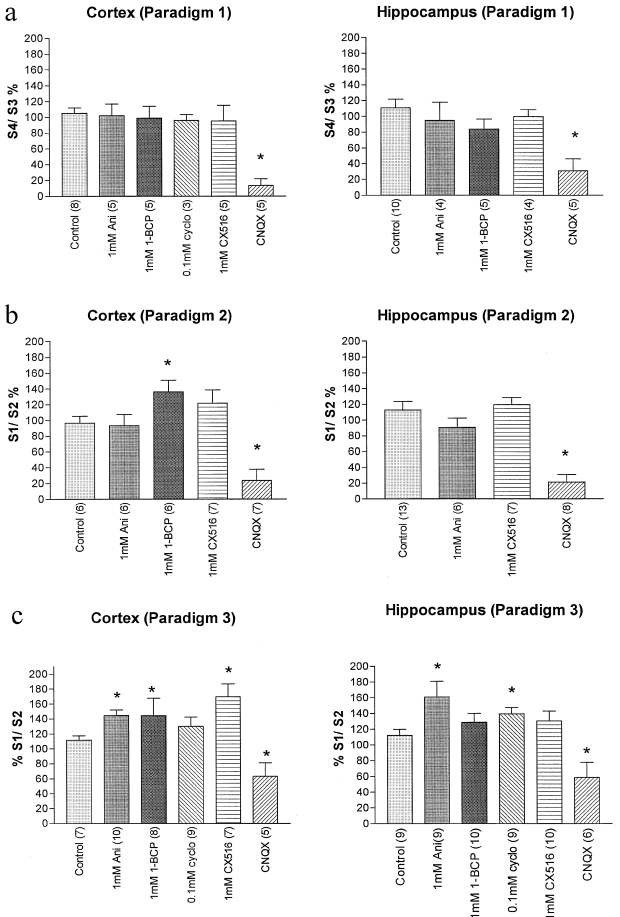

Fig. 4. (a) Effect of modulators as per Paradigm 1 (see Fig. 1c). A baseline of three AMPA responses was achieved before adding the modulator 10 min before and during the fourth AMPA exposure. Data are presented as percentage S4/S3. (b) Effect of modulators as per Paradigm 2 (see Fig. 2.). Modulators were added 10 min before and during the first AMPA exposure. Data is presented as percentage S1/S2. (c) Effect of modulators as per Paradigm 3 (see Fig. 1c). Modulators were added only during the AMPA exposure. Data is presented as percentage S1/S2. Numbers in parenthesis represent the number of different wedges utilized. $^{*}P < 0.05$, *t*-test.

in the hippocampus and cortex of a number of compounds (Fig. 4c). Unfortunately, many of the responses were rather weak. CX516 and 1-BCP, which had increased hippocampal EPSP amplitude, failed to significantly increase hippocampal responses to exogenously applied AMPA at 1 mM. Both CX516 and 1-BCP however, significantly increased AMPA responses in the cortex (Fig. 4c).

4. Discussion

Compounds that reportedly augment electrically stimulated hippocampal EPSPs by slowing desensitization also potentiate the effect of AMPA in the grease gap system under certain conditions. In the traditional, electrically stimulated, hippocampal slice preparation, aniracetam, 1-BCP and CX516 increased the EPSP amplitude, albeit at high concentrations. Cyclothiazide did not alter EPSP

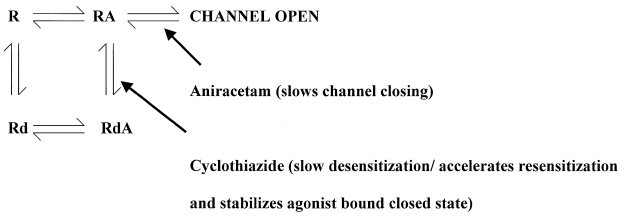

Fig. 5. Simplified kinetic scheme indicating sites and mechanism of action for cyclothiazide and aniracetam on the AMPA receptor (adapted in part from Yamada, 1998). R = receptor, A = agonist, d = desensitized state of receptor.

height. The latter is in accordance with previously reported data (Larson et al., 1994). Cyclothiazide is believed to stabilize the agonist-receptor closed state, whereas aniracetam is believed to slow the rate of channel closing (Fig. 5). Both compounds therefore attenuate the rates of desensitization but differ in mechanism and, as is highlighted by these experiments, this can have different functional outcomes. Indeed, the sites of action on the AMPA receptor of aniracetam and cyclothiazide are believed to be separate (Yamada, 1998). Therefore, a system that could functionally detect compounds having ''cyclothiazide-like'' effects as well as ''aniracetam-like'' effects would be beneficial to this area of research. In the grease gap studies using the hippocampus, cyclothiazide increased the amplitude of AMPA-induced depolarization. This was not the case, however, in the cortex. A reason for this difference could be a variation in AMPA receptor type between the two brain areas. In this regard, cyclothiazide is known to be more efficacious at the flip isoform of the AMPA receptor (Partin et al., 1994). A differential displacement of AMPA binding by cyclothiazide in the hippocampus and cortex has been recently published (Kessler et al., 1998); the authors discuss the possibility that subclasses of AMPA receptor modulators will possess pharmacological selectivity across the CNS. One might therefore suggest that flip–flop ratio is greater in the hippocampus as compared to the area of frontal cortex used in this study.

CX516 and 1-BCP demonstrated activity in the electrically stimulated hippocampus model and augmented AMPA responses in the cortex. Unexpectedly, CX516 and 1-BCP did not augment AMPA responses in the hippocampus, as they did in the electrically stimulated hippocampus model, but did augment in the cortex. It can be suggested that the state of the AMPA receptor in response to a 2-min application of AMPA is different from that in response to electrically stimulated release of glutamate. Also, using the grease gap methodology, all postsynaptic AMPA receptors present on CA1 neurons traversing the two chambers will be available for modulation of the response. In contrast, with the electrically stimulated model, only those of the Schaffer collateral–CA1 pathway will participate in the response. Therefore, a difference in AMPA receptor populations may explain the apparent discrepancy between the two systems used here.

Interestingly, the mode of application of the AMPA receptor modulators effected the outcome of the response in the grease gap system. Neither Paradigm 1 or Paradigm 2 (Fig. 1c), where the modulators were applied for 10 min prior to and during the AMPA applications, was particularly useful in uncovering modulatory activity. In contrast, co-application of modulator and AMPA (Paradigm 3) provided a more robust methodology. One can propose that because AMPA in the grease gap system is applied for 2 min, receptor desensitization is almost certainly occurring which complicates modulation of functional outcome. Also, it raises the possibility that modulators may encounter some tachyphylaxis or desensitization due to fact that pre-exposure appears to reduce activity. In some pilot experiments, AMPA modulators were applied to the electrically stimulated EPSP for long periods (approximately 15 min) but no apparent reduction of augmentation was seen (data not presented). However, as discussed above, a comparison of modulators across an electrically generated AMPA response compared to exogenously applied AMPA is difficult. In a grease gap system utilizing the cerebellum, large augmentations of AMPA-induced depolarizations were seen in response to aniracetam and cyclothiazide (Boxall and Garthwaite, 1995). These data contrast with the relatively modest effects of AMPA receptor modulators seen in this study. The Purkinje cells of the cerebellum possess GluR1, GluR2 and GluR3 subunits but not GluR4 (Wisden and Seeburg, 1993); the presence of GluR4 conveys a negative correlation of AMPA receptor desensitization (Geiger et al., 1995). Therefore, one can suggest that because the hippocampal CA1 cells possess GluR4, the proportion of AMPA receptors in the desensitized state (Fig. 5) will be greater in the hippocampus than in the cerebellum and therefore will be unable to be effected by modulators.

In summary, it has been shown that AMPA receptor modulator compounds can modestly augment AMPA responses in the medial prefrontal cortex as well as in the hippocampus under specific conditions. Interestingly, it appears that functional differences between the hippocampus and the cortex can be measured. Further research into this area could yield compounds that discriminate between AMPA receptor subtypes in different brain areas.

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