

METABOTROPIC GLUTAMATE RECEPTORS AND EPILEPTIFORM BURSTING

Differential Roles for mGluR1 and mGluR5 in the Persistent Prolongation of Epileptiform Bursts

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PURPOSE: Transient activation of group I metabotropic glutamate receptors (mGluRs) with the selective agonist (S)-3,5-dihydroxyphenylglycine (DHPG) produces persistent prolongation of epileptiform bursts in guinea-pig hippocampal slices, the maintenance of which can be reversibly suppressed with group I mGluR antagonists. To determine the relative roles of mGluR1 and mGluR5 in these group I mGluR-dependent induction and maintenance processes, subtype-selective antagonists were used. In the presence of picrotoxin, DHPG (50 μ M, 20–45 min) converted interictal bursts into 1- to 3-s discharges that persisted for hours after washout of the mGluR agonist. 2-Methyl-6-(phenylethynyl)-pyridine (MPEP, an mGluR5 antagonist; 25 μ M) and (+)-2-methyl-4-carboxyphenylglycine (LY367385, an mGluR1 antagonist; 20–25 μ M) each significantly suppressed the ongoing expression of the mGluR-induced prolonged bursts. However, LY367385 was more effective, reducing the burst prolongation by nearly 90%; MPEP produced only a 64% reduction in burst prolongation. Nevertheless, MPEP was more effective at preventing the induction of the burst prolongation; all 10 slices tested failed to express prolonged bursts both during and after coapplication of DHPG with MPEP. Coapplication of DHPG with LY367385, in contrast, resulted in significant burst prolongation (in 68% of slices tested) that was revealed on washout of the two agents. These results suggest that although both receptor subtypes participate in both the induction and maintenance of mGluR-mediated burst prolongation, mGluR1 activation plays a greater role in sustaining the expression of prolonged bursts, whereas mGluR5 activation may be a more critical contributor to the induction process underlying this type of epileptogenesis.

COMMENTARY

Elucidation of the precise mechanisms responsible for interictal-to-ictal transitions and for persistent seizure susceptibility (epileptogenesis) continues to be an area of intense research. Although multiple processes are involved, firmly establishing a causal relation for putative mechanisms, as distinguished from epiphenomena, is often difficult. However, metabotropic glutamate receptors have been shown, at least under certain circumstances, to have a causal role in seizure generation and persistence. The author of this article previously established an *in vitro* seizure model in the CA3 region of hippocampal slices. After previous exposure to the γ -aminobutyric acid subtype A (GABA_A) antagonist picrotoxin, the subsequent application of a group I metabotropic glutamate receptor (mGluR) agonist [(S)-3,5-dihydroxyphenylglycine (DHPG)] to slices effects a prolongation of ongoing interictal bursts and the development of frank spontaneous electrographic seizures. This seizure activity, once established, persists for hours, even after washout of DHPG. In this latest effort, the author explored whether the process of epileptogenesis in this model can be distinguished into induction and maintenance phases. Group I mGluRs comprise two receptor subtypes (mGluR1 and mGluR5), both of which are present in CA3, and both of which are linked to inositol-1,4,5-triphosphate (IP₃) generation and calcium mobilization (although they each generate different intracellular calcium responses). It is postulated that the mGluR1 and mGluR5 responses may be differentially responsible for the induction and maintenance processes involved in epileptogenesis.

Accordingly, the experiments explore the effects of mGluR1 and mGluR5 antagonists on induction and maintenance of the persistent seizure activity after application of DHPG. To study the induction of seizure activity, mGluR1 or mGluR5 antagonists were applied with picrotoxin, before the application of DHPG. The mGluR5 antagonist reversibly suppressed the burst prolongation usually seen with DHPG (both in its presence and after washout), but not the frequency of the bursts. The mGluR1 antagonist likewise suppressed burst prolongation in the presence of DHPG, but duration gradually increased after washout of both drugs in five (68%) of eight slices.

To examine the contribution of mGluR1 and mGluR5 in the maintenance of DHPG-induced persistent prolonged bursts, antagonists of these respective mGluRs were applied after these bursts were established. An 89% reduction in the prolongation of bursts was seen after application of the mGluR1 antagonist, and this was reversible. The mGluR5 antagonist produced a decrease in burst duration as well (64%), although burst length was more variable. The reductions by the two antagonists were shown to be statistically different from each other.

These experiments suggest that induction and maintenance phases likely exist in this experimental model of epileptogenesis. However, the results of mGluR-specific antagonism are somewhat less clear cut than one might have hoped. The data provided for induction are complex. There was complete suppression of burst prolongation in the presence of the mGluR1 or mGluR5 antagonist. For the mGluR5 blocker, this suppression was persistent on washout of the drugs, but the suppression was incomplete in a majority of the slices exposed to the mGluR1 antagonist on washout. On this basis, it

is suggested that mGluR5 is mainly responsible for the induction process; however, in about one third of slices exposed to the mGluR1 antagonist, prolonged bursts continued to be suppressed. The results of the experiments aimed at the maintenance also are complicated. Although both mGluR1 and mGluR5 antagonists suppressed the persistent prolonged bursts after DHPG washout, the mGluR1 antagonist was found to be more effective (statistically).

Although these experiments suggest that there are independent roles for mGluR1 and mGluR5 in the epileptogenic process involved in this model, the only firm conclusion one can make on the basis of the data presented would be that they have somewhat differential, but not necessarily exclusive effects on induction and maintenance. Their actions may be synergistic in each of the two phases, perhaps through their commonality of mechanisms, which involve IP_3 and calcium mobilization. These results are sure to prove of heuristic value for further, more definitive study of this model.

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