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Compensatory changes in the hippocampus of somatostatin knockout mice: upregulation of somatostatin receptor 2 and its function in the control of bursting activity and synaptic transmission

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Abstract

Somatostatin-14 (SRIF) co-localizes with γ-aminobutyric acid (GABA) in the hippocampus and regulates neuronal excitability. A role of SRIF in the control of seizures has been proposed, although its exact contribution requires some clarification. In particular, SRIF knockout (KO) mice do not exhibit spontaneous seizures, indicating that compensatory changes may occur in KO. In the KO hippocampus, we examined whether specific SRIF receptors and/or the cognate peptide cortistatin-14 (CST) compensate for the absence of SRIF. We found increased levels of both sst_2 receptors (sst_2) and CST, and we explored the functional consequences of sst_2 compensation on bursting activity and synaptic responses in hippocampal slices. Bursting was decreased by SRIF in wild-type (WT) mice, but it was not affected by either CST or sst_2 agonist and antagonist. sst_4 agonist increased bursting frequency in either WT or KO. In WT, but not in KO, its effects were blocked by agonizing or antagonizing sst_2, suggesting that sst_2 and sst_4 are functionally coupled in the WT hippocampus. Bursting was reduced in KO as compared with WT and was increased upon application of sst_2 antagonist, while SRIF, CST and sst_2 agonist had no effect. At the synaptic level, we observed that in WT, SRIF decreased excitatory postsynaptic potentials which were, in contrast, increased by sst_2 antagonist in KO. We conclude that sst_2 compensates for SRIF absence and that its upregulation is responsible for reduced bursting and decreased excitatory transmission in KO mice. We suggest that a critical density of sst_2 is needed to control hippocampal activity.

Introduction

In the hippocampus, somatostatin-14 (SRIF) is present in distinct interneurons and acts in concert with γ-aminobutyric acid (GABA), with which it is co-localized and sometimes co-released (Binaschi *et al*., 2003; Jinno & Kosaka, 2004; Matyas *et al*., 2004). The acute effects of SRIF on excitatory transmission are largely modulatory and include a powerful inhibition of excitation (Baraban & Tallent, 2004).

The involvement of SRIF in the control of seizures and epileptogenesis has been proposed for some time (Tallent & Siggins, 1997, 1999; Vezzani & Hoyer, 1999; Binaschi *et al*., 2003; Baraban & Tallent, 2004). However, there are conflicting reports in the literature and there is a need for clarification, particularly with respect to the contribution of the specific SRIF receptors (sst_{1-5}) mediating the actions of SRIF (Binaschi *et al*., 2003; Thermos *et al*., 2006). For example, in rat models of temporal lobe epilepsy, the sst_2 receptor mediates the anticonvulsant effects of SRIF (Perez *et al*., 1995), whereas it does not mediate SRIF's inhibition of excitatory neurotransmission and seizures in mice (Moneta *et al*., 2002). In addition, sst_4 receptors mediate seizure increase in mice and interact functionally with sst_2 receptors (Moneta *et al*., 2002). Using a mouse acute model of interictal-like activity, we recently demonstrated that sst_2 receptors do not mediate SRIF's inhibition of hippocampal bursting (Cammalleri *et al*., 2004).

In a study addressing whether the absence of SRIF results in seizures, Buckmaster *et al*. (2002) observed that SRIF knockout (KO) mice do not exhibit spontaneous seizures and that their seizure severity is only slightly worse than in wild-type (WT) mice. These data suggest that SRIF may be, at best, only mildly anticonvulsant, in contrast to what may be predicted from previous studies (Vezzani & Hoyer, 1999; Binaschi *et al*., 2003). A possible explanation for the lack of more dramatic effects on seizures in SRIF KO mice is that distinct SRIF receptors compensate functionally for the absence of SRIF. Indeed, there is evidence that SRIF significantly contributes to the regulation of expression of its receptors (especially for the sst_2 receptor, Csaba *et al*., 2004). Furthermore, in SRIF KO mice, brain levels of SRIF receptors, and in particular of the sst_2 receptor, are increased (Ramirez

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