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Somatostatin receptors differentially affect spontaneous epileptiform activity in mouse hippocampal slices

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Abstract

Somatostatin-14 [somatotropin release-inhibiting factor (SRIF)] reduces hippocampal epileptiform activity but the contribution of its specific receptors (sst_{1-5}) is poorly understood. We have focused on the role of sst_1 and sst_2 in mediating SRIF modulation of epilepsy using hippocampal slices of wild-type (WT) and sst_1 or sst_2 knockout (KO) mice. Recordings of epileptiform discharge induced by Mg^{2+}-free medium with 4-aminopyridine were performed from the CA3 region before and after the application of SRIF compounds. In WT mice, SRIF and the sst_1 agonist CH-275 reduce epilepsy whereas sst_1 blockade with its antagonist SRA-880 increases the bursting discharge. Activation of sst_2 does not affect the bursting frequency unless its agonist octreotide is applied with SRA-880, indicating that sst_1 masks sst_2-mediated modulation of epilepsy. In sst_1 KO mice: (i) the bursting frequency is lower than in WT; (ii) SRIF, CH-275 and SRA-880 are ineffective on epilepsy and (iii) octreotide is also devoid of effects, whereas blockade of sst_2 with the antagonist D-Tyr^8 Cyn 154806 increases the bursting frequency. In sst_2 KO mice, the SRIF ligand effects are similar to those in WT. In the whole hippocampus of sst_1 KO mice, sst_2 mRNA, protein and binding are higher than in WT and reverse transcription-polymerase chain reaction of the CA3 subarea confirms an increase of the sst_2 messenger. We conclude that sst_1 mediates inhibitory actions of SRIF and that interactions between sst_1 and sst_2 may prevent sst_2 modulation of epilepsy. We suggest that, in sst_1 KO mice, activation of over-expressed sst_2 reduces the bursting frequency, indicating that sst_2 density represents the rate-limiting factor for sst_2-mediated modulation of epilepsy.

Introduction

Somatostatin-14 [somatotropin release-inhibiting factor (SRIF)] is a neuropeptide widely distributed in different brain regions, including the hippocampal formation (Binaschi *et al.*, 2003). SRIF actions are mediated by five receptor subtypes (sst_{1-5}). In the rodent brain, receptor binding studies and immunological analysis have shown a widespread but selective distribution of distinct SRIF receptors (Schulz *et al.*, 2000; Weckbecker *et al.*, 2003). SRIF receptors are coupled to G proteins and trigger multiple transmembrane signalling systems (Lahlou *et al.*, 2004) mediating different functions of SRIF receptors which also depend on their possible interactions. For example, in recombinant systems, $sst_{2/3}$ and $sst_{1/5}$ receptor interactions have been demonstrated (Rocheville *et al.*, 2000; Pfeiffer *et al.*, 2001). However, little is known about native systems. In particular, functional interactions have been suggested between sst_2 and sst_5 receptors in rat tumour somatotrophs (Cervia *et al.*, 2003c). In addition, sst_2 and sst_4 receptors appear to be functionally coupled in the mouse hippocampus (Moneta *et al.*, 2002). Finally, interactions between sst_1 and sst_2 receptors have recently been suggested in the mouse retina (Pavan *et al.*, 2004).

At the neuronal level, SRIF is involved in multiple functions, including control of excitatory neurotransmission. In the rat hippocampus, SRIF inhibits neuronal excitability by affecting Ca^{2+} and K^+ conductances (Boehm & Betz, 1997; Schweitzer *et al.*, 1998; Baraban & Tallent, 2004). In addition, there is evidence indicating that SRIF, possibly released by SRIF-containing interneurones participating in the lateral inhibitory circuits in the dentate gyrus (Buckmaster *et al.*, 2002; Kobayashi & Buckmaster, 2003), reduces epileptiform activity in both CA1 and CA3 hippocampal regions (Tallent & Siggins, 1997, 1999; Vezzani & Hoyer, 1999; Baraban & Tallent, 2004). These observations suggest that SRIF plays a role in seizure control and therefore that it may have an importance as a potential therapeutic agent for temporal lobe epilepsy (Vezzani & Hoyer, 1999; Binaschi *et al.*, 2003).

Information on the precise contribution of each SRIF receptor subtype on the SRIF-induced inhibition of epileptiform activity is still limited. Of the five SRIF receptors, the sst_2 receptor is the candidate likely to mediate the anticonvulsant effects of SRIF in the hippocampus and entorhinal cortex of rats (Vezzani & Hoyer, 1999). Previous findings, however, have demonstrated that, in mice, these receptors do not mediate inhibitory effects of SRIF on seizure susceptibility and hippocampal excitatory neurotransmission. Rather, excitatory actions of sst_4 receptors have been reported (Moneta *et al.*, 2002).

No information is available on the sst_1 receptor function in hippocampal physiology. In the rodent hippocampus, for instance, the expression of sst_1 receptors has not been conclusively demonstrated using either immunohistochemistry or radioligand binding (Hervieu & Emson, 1998; Schulz *et al.*, 2000; Videau *et al.*, 2003), whereas previous studies have suggested that hippocampal neurones may express sst_1 receptor mRNA (Perez *et al.*, 1994; Hannon *et al.*, 2002b).

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