Somatostatin Depresses Long-Term Potentiation and Ca^{2+} Signaling in Mouse Dentate Gyrus

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INTRODUCTION

A consistent finding in postseizure hippocampus, in both tissue removed from humans with epilepsy and in animal models, is the highly selective loss of somatostatin (SST)-containing interneurons in the hilus of the dentate gyrus (de Lanerolle et al. 1989; Robbins et al. 1991; Sloviter 1987). These are GABAergic neurons with projections and inputs that have been characterized in detail. These neurons receive input from both mossy fiber collaterals of dentate granule cells and from perforant path (Leranth et al. 1990) and project in a highly defined pattern to distal dendrites of granule cells in the outer molecular layer (Milner and Bacon 1989). The SST-containing interneurons appear to form synapses on spines adjacent to perforant path synapses, thus they are critically localized to regulate the major input into the dentate from entorhinal cortex. SST terminals are found in the hilus as well (Leranth et al. 1990; Milner and Bacon 1989). Based on these anatomical considerations, it has been speculated that SSTergic interneurons mediate feedback inhibition in the dentate. However, the death of these neurons failed to be correlated with any deficit in feedback inhibition in animal models of epilepsy (Buckmaster and Dudek 1997). Thus it remains unclear how loss of somatostatinergic neurons contributes to the pathophysiology of seizure-induced hyperexcitability in the dentate.

Intracerebroventricular and intrahippocampal injections of SST and SST analogs have been shown to modulate seizure activity in animal models. Although some early studies suggested that SST had augmenting actions on seizures (Higuchi et al. 1983; Perlin et al. 1987), more recent studies, including those in which SST was directly injected into hippocampus, have revealed robust inhibitory actions on behavioral and electrical seizures recorded in vivo (Perez et al. 1995; Vezzani et al. 1991, 2000). At the cellular level, SST also has inhibitory effects in CA1 and CA3 regions of the hippocampus in vitro. In CA1, SST activates postsynaptic K^{+} currents in pyramidal neurons (Moore et al. 1988; Schweitzer et al. 1998) to hyperpolarize neurons away from their threshold for firing. SST inhibits glutamatergic excitatory postsynaptic currents (EPSCs) at CA1 Schaeffer collateral synapses, while not affecting GABAergic inhibitory postsynaptic currents (Boehm and Betz 1997; Tallent and Siggins 1997). In CA3, SST inhibits EPSCs generated at associative/commissural synapses while not affecting mossy fiber EPSCs (Tallent and Siggins 1999). Using in vitro seizure models, we showed that SST inhibits epileptiform bursting and evoked afterdischarges in both CA1 and CA3 (Tallent and Siggins 1999).

Thus, although the actions of SST have been characterized in CA1 and CA3 hippocampus, its actions in dentate remain unknown. We therefore chose to examine the actions of SST in the dentate of the mouse using electrophysiological methods, with the goal of addressing the functional consequence of the loss of SST function in epileptic hippocampus. Although much of the previous work on SST actions in hippocampus was done in rat, we chose to use the mouse as a model, with the future goal of studying SST actions in transgenic/knockout mice. Some of the data presented here have been published in abstract form (Tallent et al. 1999, 2000).

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METHODS

All mouse experiments were performed in accordance with institute and National Institutes of Health guidelines on the care and use of laboratory animals. We similarly prepared hippocampal slices to our previous description for rat (Pittman and Siggins 1981; Schweitzer et al. 1993), with some modifications. Briefly, male mice (5–10 wk) were anesthetized with halothane (4%) and decapitated, and the brains rapidly removed and placed in ice-cold artificial cerebrospinal fluid (ACSF), gassed with 95% O₂-5% CO₂ (carnogen), of the following composition (in mM): 130 NaCl, 3.5 KCl, 1.25 NaH₂PO₄, 1.5 MgSO₄, 7H₂O, 2 CaCl₂·2H₂O, 24 NaHCO₃, and 10 glucose. We cut horizontal brain slices (400 μm) using a Campden vibrisscator or a Vibratome Series 3000 (Technical Products International, St. Louis, MO). Hippocampal formations and adjacent entorhinal cortex were dissected from the slices and incubated in the recording chamber for 20 min with their upper surfaces exposed to warmed, humidified carbone. The slices were submerged and continuously superfused with warm (31°C), gassed ACSF at a constant rate (2–3 ml/min) for the remainder of the experiment. The inner chamber had a total volume of 1 ml; at the superfusion rates used, 90% replacement of the chamber solution could be obtained within 1–1.5 min. Drugs and peptides were added to the bath from stock solutions at known concentrations. We obtained SST from Bachem (Torrance, CA) or Anaspec (San Jose, CA). (-)-2-amino-phosphonovaleric acid (APV) and 6-cyano-7-nitroquinoline-2,3-dione (CNQX) were purchased from Tocris (St. Louis, MO) and ω-conotoxin GVIA from Anaspec. All other chemicals were from Sigma (St. Louis, MO).

Extracellular recording

We acquired data with an Axoclamp 2A or 2B amplifier (Axon Instruments) by D/A sampling using pCLAMP acquisition software (Axon Instruments). Extracellular field EPSPs (fEPSPs) were recorded in the outer one-third of the molecular layer (OML) of the inner blade of the dentate using a glass micropipette filled with 3 M NaCl. We evoked lateral perforant path (LPP) synaptic responses at 30 ms. Only responses that showed full field amplitude for 20 ms following the trains. HFTs. For studies of LTP maintenance, SST was administered and during the same week as the drug.

Statistics

We used ANOVA with or without repeated measures using CRUNCH software (CRUNCH Software Corporation) or EXCEL (Microsoft) to determine statistical significance at P < 0.05. For LTP, we measured differences across the last 15 min of trials (45–60 min post HFTs). For posttetanic potentiation, we analyzed 1–5 min following the trains.

RESULTS

SST does not inhibit LPP fEPSPs

When LPP EPSPs were evoked by a single test stimulus, 1 μM SST did not consistently alter the amplitude or area of the event. In three of seven slices we saw a moderate inhibition of <15%. The overall effect of SST on fEPSPs recorded at different stimulus strengths was not statistically significant (P > 0.1; n = 7), although there is a trend toward a decrease at the lowest stimulus intensity (Fig. 1A). Application of SST did not alter paired-pulse facilitation of fEPSPs tested at interstimulus intervals ranging from 15 to 100 ms. Shown in Fig. 1B, left, are representative pairs of fEPSPs generated at 50-ms intervals using a half-maximal stimulus intensity. SST (1 μM) superfusion did not alter the degree of facilitation. Mean data from seven slices is shown in Fig. 1B, right. No significant effect on facilitation of fEPSP initial slope is observed at any of the interstimulus intervals (P > 0.5). A lower concentration of SST (0.2 μM) also did not significantly affect fEPSP slope or amplitude (n = 12, see Fig. 2A baseline).
SST inhibits induction/stabilization but not maintenance of LTP

When 200 nM SST was applied 7–8 min prior to application of LTP-generating trains of stimuli, posttetanic potentiation in the first 5 min following the trains was unchanged (P > 0.05) but LTP was depressed (P < 0.001; n = 12). Instead of the normal decay to a plateau level within the first 15 min seen in control slices (Fig. 2, left; n = 15), when SST was applied during the induction phase, the fEPSPs never attained a stable potentiated level and instead slowly decayed back to baseline levels. By 32 min following HFTs, the fEPSP slope was 104 ± 7.9% of baseline. By 8 min following HFTs, the fEPSP slope from slices where SST had been applied and washed out was significantly less than in control slices. A higher concentration of SST produced less consistent responses. LTP was blocked (60% of baseline 60 min following HFTs) in 6 of 12 slices exposed to 1 μM SST prior to HFTs. However, in all 12 slices there was not a significant effect overall (not shown). In the 6 slices in which LTP was reduced, this concentration of SST also significantly reduced posttetanic potentiation in the first 5 min following the train (not shown).

To examine the action of SST on maintenance of LTP, we established LTP in control ACSF and superfused 200 nM SST from 30 to 45 min following HFTs. After LTP was established, superfusion of SST did not affect its maintenance (Fig. 2, right; n = 7). Prior to beginning SST application 30 min following HFTs, fEPSP slopes were 146 ± 4% of baseline. At the end of the SST superfusion (45 min post-HFTs), fEPSP slopes were 143 ± 9% of baseline, and, at 60 min post-HFTs, fEPSP slope was 147 ± 8% of baseline. Thus SST did not cause a decrement of the fEPSP slope after LTP had stabilized.

Since SST did not appear to inhibit LPP fEPSPs, we further examined the mechanism by which SST blocked stabilization of LTP. Since LTP at this pathway is NMDA receptor dependent, we examined whether SST could block isolated NMDA receptor–mediated fEPSPs. To isolate NMDA receptor–mediated fEPSPs, we superfused 200 nM SST from a representative experiment showing LTP is preserved following superfusion of SST 30–45 min following trains.
SOMATOSTATIN DEPRESSES DENTATE LTP

To determine whether SST could reduce postsynaptic excitability by augmenting noninactivating K⁺ currents, as in CA1 hippocampus, we used intracellular voltage-clamp techniques to analyze SST actions on postsynaptic currents. In the presence of TTX, we evoked currents by stepping the membrane potential from about −70 mV to a range of voltages from −120 to −40 mV. We found that SST (1 μM) had no significant action on currents active in this voltage range (Fig. 4; n = 5). In three neurons voltage clamped using whole-cell patch-clamp, SST also did not affect postsynaptic currents (not shown).

SST does not act on sustained postsynaptic currents in dentate granule cells

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SST depresses Ca²⁺ spikes in dentate granule cells

Because of difficulty in recording Ca²⁺ currents in the slice preparation and the unsuitability of our studies to use of acutely isolated neurons (see DISCUSSION) to determine possible actions of SST on Ca²⁺ conductances we examined Ca²⁺/Ba²⁺ spikes evoked by depolarizing current steps and recorded in current-clamp in 1–2 μM TTX, 300–600 μM Ba²⁺, and 1 mM TEA. These spikes were sensitive to superfusion of 500 μM Cd²⁺ (Fig. 5C). We found that Ca²⁺ spikes were inhibited by 0.2 to 1 μM SST. In seven neurons tested, 1 μM SST reduced the number of spikes generated at a given membrane potential. SST inhibited the number of spikes evoked by depolarizing the neuron to between −45 and −40 mV from 2.1 ± 0.4 to 0.9 ± 0.3 (P < 0.05), representing a reduction of 57%. This action was reversible on washout in five neurons. In most neurons, SST blocked spiking at current injection amplitudes just above threshold and reduced the number of spikes per step with increasing depolarization. Unlike its effect on LTP, 1 μM SST was more potent than 200 nM in reducing the number of spikes (n = 5), with only a 35 ± 18% reduction in firing rate during a depolarization between −45 and −40 mV with the lower concentration. To determine whether SST was acting directly on a Ca²⁺ current, we tested whether subtype-selective Ca²⁺ channel blockers could block SST inhibition of spikes. Ca²⁺ spikes could still be generated in the presence of L-, T-, and N-type channel blockers (Fig. 5A). SST (1 μM) inhibited Ca²⁺ spikes in the presence of 10 μM nifedipine (L-type blocker; n = 6; Fig 5A) and 50 μM nickel (T-type blocker; n = 6; Fig. 5B). Multiple spikes could not be

FIG. 3. SST moderately depresses pharmacologically isolated N-methyl-D-aspartate (NMDA) iEPSPs but not voltage-clamped NMDA EPSCs. A: Left: NMDA iEPSPs recorded in outer molecular layer in 6-cyano-7-nitroquinolinic acid-2,3-dione disodium (CNQX, 30 μM) and Mg²⁺-free artificial cerebrospinal fluid at threshold, half-maximal, and maximal stimulus intensities. SST (1 μM) moderately depresses the iEPSPs in a reversible manner. Right: mean effect of SST on NMDA iEPSP quantified using coastline burst index (CBI). Addition of 250 nM ω-conotoxin 25–30 min prior to SST effectively blocks the effect of the peptide. B: Left: representative NMDA EPSCs recorded from dentate granule cells using whole-cell voltage-clamp. SST does not affect the EPSCs. Right: mean data showing no significant effect of SST on NMDA EPSC amplitude at three different stimulus intensities (n = 4).
transmitter release (Luebke et al. 1993; Takahashi and Moriyama 1993). When ω-conotoxin was applied 20 min prior to HFS, LTP was significantly reduced, even when stimulus strengths were normalized to generate 30–50% of maximal responses (Fig. 5D; n = 7). These results suggest that influx of Ca$^{2+}$ through N-type Ca$^{2+}$ channels contributes to LTP at LPP synapses. To verify that our stimulus paradigm evoked an LTP that was dependent on activation of NMDA receptors, as has previously been reported for this synapse (Colino and Malenka 1993; Xie and Lewis 1995), we superfused 30 μM APV prior to application of trains. No LTP was generated in these three slices (Fig. 5D), confirming our protocol induces NMDA receptor–dependent LTP. We also tested whether ω-conotoxin could block the SST inhibition of the NMDA fEPSP, since this did not appear to be a direct effect on NMDA receptors (see DISCUSSION). The SST effect was largely blocked when 250 nM ω-conotoxin was applied 25–30 min prior to superfusion of SST (Fig. 3A; n = 6, P < 0.005).

DISCUSSION

We show here that SST blocks induction of LPP LTP when applied prior to and during LTP-generating HFTs. SST does not affect LTP after its establishment and does not have apparent direct effects on standard synaptic responses recorded extracellularly or intracellularly. These results suggest that SST is not likely acting presynaptically to inhibit glutamate release. SST binding is dense in the outer molecular layer, and SST receptors appear to be expressed on distal dendrites of dentate granule cells and not presynaptically on LPP terminals (Schindler et al. 1997). Therefore SST is likely acting at a postsynaptic site to affect synaptic potentiation.

Previous studies have suggested that SST facilitates LTP at some synapses in the hippocampus. An in vitro study in guinea pig demonstrated that SST augmented mossy fiber LTP in CA3 neurons (Matsuoka et al. 1991). In dentate, a previous in vivo study in rat suggested facilitation by SST of medial perforant path LTP (Nakata et al. 1996). Thus SST may have different effects at different hippocampal synapses; however, species differences cannot be ruled out. Our previous studies in rat have demonstrated only inhibitory actions of SST in CA1 and CA3 at the cellular and network level (Tallent and Siggins 1997, 1999). Likewise, most in vivo studies in rat suggest that SST reduces hyperexcitability in hippocampus (Perez et al. 1995; Vezzani et al. 1991, 2000).

The localization of SST receptors on distal dendrites of dentate granule cells makes it technically difficult to determine the action of SST in these neurons using intracellular recording techniques. It is possible that changes in cellular properties induced by SST in distal dendrites would not be reflected at the cell soma, where recording electrodes are located. Likewise, voltage clamping in the soma is unlikely to extend to distal dendrites (Spruston et al. 1993), thus it is difficult to determine current-voltage properties in these regions. Techniques typically used to minimize such space-clamp problems, such as studying acutely dissociated dentate granule cells, are not appropriate in our studies, because of the localization of SST receptors in distal dendrites, which are not preserved in this preparation. Future studies will address these issues by directly recording from distal dendrites.

We found no postsynaptic action of SST on K$^+$ currents nor...
did we detect any hyperpolarizing action of SST on dentate granule cells. This is in contrast to previously reported actions of SST in CA1 and CA3 hippocampus (Moore et al. 1988; Pittman and Siggins 1981; Schweitzer et al. 1998; Tallent and Siggins 1999). We also previously showed that SST inhibits excitatory neurotransmission in CA1 and CA3 pyramidal neurons. NMDA and AMPA/KA-mediated EPSCs recorded at both Schaeffer collateral/CA1 synapses and associational/commissural CA3 synapses are inhibited by SST (Tallent and Siggins 1997, 1999). These actions of SST are likely presynaptic, as corroborated by a study in cultured hippocampal pyramidal neurons showing SST inhibited glutamate but not GABA release (Boehm and Betz 1997). In contrast, we detected no presynaptic action of SST at LPP/dentate granule synapses.

It is possible that differences between hippocampal regions are due to distinct localization of SST receptors in each region. In CA1 and CA3, SST receptors are located in stratum radiatum and to a lesser extent in the stratum pyramidale (Leroux et al. 1993). Thus SST actions recorded at the soma are likely to be less “filtered” by the cable properties of the dendrites than responses recorded in dentate granule cells, where SST receptor expression occurs mostly in the distal dendrites. Also, the pattern of expression of SST receptor subtypes may be different between these regions. Immunohistochemistry studies in rat indicate that SST1 density is greater in dentate than CA1 (Hervieu and Emson 1998), whereas SST4 expression is similar in both regions (Schreff et al. 2000). SST2 expression was shown by one group to be greater in CA1 than dentate (Dournaud et al. 1996), whereas another group using a different antibody reported a higher density in dentate (Schindler et al. 1997). SST3 immunohistochemistry has not yet been reported, although in rat its mRNA is expressed in both CA1 and dentate (Kaupmann et al. 1993; Thoss et al. 1995). Each of these receptors may couple to a distinct repertoire of effectors (Schonbrunn 1999); however, the actions of these different receptor subtypes in central neurons are not well characterized (Csaba and Dournaud 2001).

Immunohistochemical localization of SST receptors has not been reported for mouse, although in situ hybridization demonstrated high levels of mRNA expression for SST1-4 in mouse dentate granule cells (Jinno and Kosaka 2000). In rat, most immunohistochemistry studies have confirmed postsynaptic expression of receptors in dentate, especially on dentate

FIG. 5. Ca2+ spikes recorded from dentate granule cells. A: when slices were previously treated with the L-type channel blocker nifedipine (10 μM) for 20 min, SST (1 μM) still depressed Ca2+ spikes. B: in the presence of 50 μM nickel, SST (1 μM) was able to inhibit Ca2+ spikes. C: no inhibition of Ca2+ spikes by SST was seen in the presence of 250 nM ω-conotoxin. D: LTP expression is reduced when 250 nM ω-conotoxin is applied beginning 20 min prior to trains (n = 7). When 20 μM d-2-aminophosphonovaleric acid (APV) is applied beginning 20 min prior to trains, no LTP is generated (n = 3).
granule cell dendrites. SST$_1$ protein is localized largely in the granule cell layers on cell somas (Hervieu and Emson 1998). For SST$_2\beta$, one group reported dense expression on granule cell dendrites (Schindler et al. 1997), while another group using a different antibody reported presynaptic localization (Dournaud et al. 1996). SST$_2\alpha$ is localized postsynaptically on dendrites of dentate granule cells (Schindler et al. 1999). SST$_4$ is also expressed on dendrites of dentate granule cells, as well as on processes of SSTergic interneurons in the hilus (Schreft et al. 2000). These anatomical observations therefore support our findings of a postsynaptic action for SST in dentate, although the current study does not address receptor subtype specificity.

Interestingly, in rats but not mice (Buckmaster et al. 1994; Jinno and Kosaka 2000), the outer molecular layer is densely innervated by terminals of SSTergic interneurons. Thus in mice there may be a mismatch between the location of peptide and receptors. Such a mismatch is not uncommon for peptides and their receptors (see for example Schindler et al. 1999) and suggests that peptides may diffuse away from their site of release and exert effects on distal targets (Elde et al. 1995). Also, there is increasing evidence that peptides are released extrasynaptically; for example, dendritic release of dynorphin has been reported in dentate gyrus (Simmons et al. 1995).

SST effects on LTP were more consistent at 0.2 than 1 $\mu$M, although in slices in which the higher concentration was effective its action was more robust, reducing both posttetanic potentiation as well as LTP. This difference could be due to desensitization of SST receptors at the higher concentration. However, in CA1 and CA3, 1 $\mu$M SST produces maximal effects on regulating both postsynaptic $K^+$ currents and EPSCs (Tallent and Siggins 1997, 1999). Also, in dentate, SST has a greater action on Ca$^{2+}$ spikes at 1 than at 0.2 $\mu$M, and this action of SST did not rapidly desensitize during a single application of the higher concentration. Another possibility is that the higher concentration interacts with multiple receptor subtypes that have different effects. For example, SST$_1$ and SST$_3$ have opposing effects in hypothalamus (Lanneau et al. 1998), and both these subtypes are present in dentate gyrus.

We found that SST modestly depressed pharmacologically isolated NMDA EPSPs recorded in Mg$^{2+}$-free ACSF. However, when we recorded NMDA receptor–mediated EPSCs in voltage-clamp, we observed no effect of SST. These results suggest that SST is not likely directly acting on NMDA responses. Instead, SST may be acting on voltage-sensitive conductances (i.e., Ca$^{2+}$) activated during the depolarizing EPSP. Accordingly, when SST was applied in the presence of $\omega$-conotoxin, little inhibition was observed. In any case, this modest effect on the NMDA-mediated EPSP is unlikely to account for SST inhibition of LTP, since a much greater reduction of the NMDA response is necessary to block LTP (Blake et al. 1988; Grunze et al. 1996; Rosenblum et al. 1999).

SST may regulate LTP by inhibiting N-type Ca$^{2+}$ currents, an action that has been demonstrated for SST in acutely dissociated and cultured hippocampal pyramidal neurons (Boehm and Betz 1997; Ishibashi and Akaika 1995). LPP LTP induced by high-frequency trains is an NMDA receptor–dependent event, similar to LTP in CA1 but not CA3. Dendritic L-type Ca$^{2+}$ channels are thought to be involved in an NMDA-independent type of LTP in CA1 (Huang and Malenka 1993). The involvement of Ca$^{2+}$ channels in LPP LTP has not previously been demonstrated. Our data suggest that LPP LTP evoked by a relatively moderate, nonsaturating stimulus paradigm involves entry of Ca$^{2+}$ through both N-type Ca$^{2+}$ channels and NMDA receptors. However, since N-type channels are involved in glutamate release, a presynaptic site of action for $\omega$-conotoxin cannot be ruled out. Blockade of N-type channels does not, however, influence presynaptically generated LTP at mossy fiber/CA3 synapses (Castillo et al. 1994), nor does it block CA1 LTP (Schulz 1997; Szinyei et al. 1999). Therefore a synapse-specific effect is indicated in dentate that could be postsynaptic. Postsynaptic N-type Ca$^{2+}$ channels have similarly been implicated in the induction of long-term depression in CA1 (Normann et al. 2000).

Multiple inhibitory neuropeptides depress dentate gyrus LTP. An in vivo study showed neuropeptide Y (NPY)-mediated inhibition of dentate LTP (Whittaker et al. 1999), whereas in vitro studies have shown nociceptin (Yu and Xie 1998), dynorphin (Terman et al. 1994), galanin, and cortistatin (unpublished observations) to depress LTP at LPP synapses. Some of these peptides robustly depress baseline perforant-path fEPSPs (i.e., dynorphin, nociceptin); these peptides likely have a presynaptic site of action in inhibiting glutamate releases, although they could also act postsynaptically (Yu and Xie 1998). Galanin (unpublished observations) and NPY (Klapstein and Colmers 1993; McQuiston et al. 1996), like SST, do not consistently inhibit baseline EPSPs at this synapse. NPY inhibits N-type Ca$^{2+}$ currents and Ca$^{2+}$ transients in dentate granule cells (McQuiston et al. 1996); thus, like SST, this is a possible mechanism through which this peptide could attenuate LTP. In contrast, opiate peptides acting on delta and mu receptors have facilitory actions on dentate LTP, through inhibition of GABAergic interneurons (Bramham et al. 1988, 1991; Xie and Lewis 1991). Interestingly, the excitatory neuropeptide corticotropin-releasing factor (CRF) has direct LTP-like actions on dentate granule cells in vivo (Wang et al. 2000). These results suggest a role for neuropeptides as important regulators of synaptic plasticity in dentate gyrus. Inhibition of synaptic potentiation at this synapse could be one mechanism through which some peptides diminish seizure events in models of temporal lobe epilepsy, since LTP at this synapse may contribute to invasion of seizures into hippocampus (Sutula and Stewart 1986, 1987; Wasterlain et al. 1999).

Our results suggest SST is released during high-frequency activation of SST containing interneurons and acts to prevent LTP of LPP synapses. Seizure events have been shown to cause intense activation of SST/GABAergic hilar interneurons (Vezzani et al. 1996). Thus the seizure-induced death of these neurons would lead to the loss of an important regulatory mechanism in the dentate that could contribute to the increased susceptibility of the dentate to invasion by subsequent seizures.

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REFERENCES


