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Somatostatin: An endogenous antiepileptic

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Abstract

The neuropeptide somatostatin is highly expressed in brain regions associated with seizures. In hippocampus, SST expression and release is regulated by seizures, and SST-containing neurons within the hilus of the dentate gyrus are sensitive to seizure-induced death. In vivo and in vitro studies suggest that the loss of SST function in the dentate could contribute to epileptogenesis and seizure susceptibility. SST also has inhibitory actions in the CA1 and CA3 hippocampus, indicating this peptide is an important homeostatic regulator throughout the hippocampus. In vivo studies show SST has robust antiepileptic properties, with the major site of action being hippocampus. In rodents, somatostatin receptor subtype 2 (SST_2) and SST_4 appear to mediate the majority of the antiepileptic actions of SST, with SST_2 predominate in rat and SST_4 in mouse. Thus SST receptors may be appropriate targets for new antiepileptic drugs, although validation in human tissue is lacking.

Keywords

somatostatin; cortistatin; epilepsy; seizures; neuropeptides; hippocampus; antiepileptic

Epilepsy, seizures, and treatment

Epilepsy is a disease affecting 45–100 million people worldwide and 2–3 million in the United States. The yearly economic cost to the United States of this devastating disease has been estimated at $12.5 billion, largely due to unemployment and lost earning power (Begley et al., 2000). There are two forms of seizures: generalized and partial. Generalized seizures involve both hemispheres of the brain at the time of onset. They lead to loss or impairment of consciousness. Partial seizures are confined to a single region of the brain and are further classified as simple (consciousness intact) and complex (consciousness impaired) seizures. Partial seizures can sometimes progress to generalized seizures. Temporal lobe seizures are the most common type of complex partial seizure and involve the hippocampus. The most typical pathologic abnormality of those patients is Ammon's horn sclerosis or mesial temporal sclerosis, which involves a loss of hippocampal neurons (Schwartzkroin, 1994; Swanson, 1995). Temporal lobe seizures are also the most resistant to the currently available antiepileptic

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drugs (AEDs), with as many as 40% of patients having break-through seizures (Devinsky, 2004).

The mainstay for treating epilepsy is pharmacotherapy. AEDs increase inhibition, decrease excitation, or prevent aberrant burst-firing of neurons. The major targets of the currently available AEDs are GABA receptors, Na^+ and Ca^{2+} channels, and to a lesser degree, glutamate receptors. Many of these drugs are pleiotropic in that they act on multiple targets. Some newer drugs have novel targets, for example, levetiracetam binds specifically to a presynaptic vesicular protein that affects neurotransmitter release (Lynch, 2004). Another drug in Phase II clinical trials, retigabine, is an opener of the K+ M-channel. Mutations in Kv7 subunits, that comprise M-channels, cause a human epilepsy (Charlier et al., 1998; Singh et al., 1998).

The best treatment plan for epilepsy is monotherapy, given possible adverse effects with combined therapy. However, despite the existence of many antiepileptic drugs, a third of people who develop epilepsy continue to experience seizures (Kwan and Brodie, 2004), even with polytherapy. For most of these individuals, in particular those who are not candidates for curative surgery, the only hope for improving seizure control are new drugs. New agents are badly needed that are directed at disease modification and seizure control.

Somatostatin and epilepsy

Somatostatin (SST) has been implicated as playing a prominent role in epilepsy (Vezzani and Hoyer, 1999). This hypothesis is based on persuasive experimental observations including:1) activity-dependent release of SST during seizures; 2) the modulation of SST mRNA expression, peptide levels and receptors by seizures; 3) the effect of SST and its analogues on seizures. The focus of this review will be on current knowledge on the role of SST in seizure control, and the potential targeting of SST receptors in the treatment of epilepsy, including potential pitfalls.

Seizures induce the loss of SST-containing interneurons in the dentate gyrus

The first link between SST and seizures occurred when Sloviter noted a highly selective loss of SST-containing neurons in the hilus of the dentate gyrus after repetitively induced seizures in rat (Sloviter, 1987). Shortly thereafter, this specific pattern of neuron loss was confirmed in humans with temporal lobe epilepsy (de Lanerolle et al., 1989), and an upregulation of SST binding sites in human tissue was also noted (Robbins et al., 1991). Since these first reports, the loss of SST-containing hilar interneurons has been observed in many animal models, including kainate (Buckmaster and Dudek, 1997; Sperk et al., 1992) and pilocarpine (Choi et al., 2007; Kobayashi and Buckmaster, 2003), and is now considered a hallmark of epileptic hippocampus. In as little as 2 days after kainate injection, SST-positive neurons were dramatically decreased in the inner part of the hilus, while the number of SST-positive neurons remained unchanged in nearby polymorphic cell areas (Buckmaster and Dudek, 1997). Pretreatment of rats with the SST-related peptide cortistatin (CST) is protective against both seizures and SSTergic neuronal loss (Braun et al., 1998). Most studies have reported little to no decrease in SST-containing neurons in cornu ammonis, although in more severe seizure models these neurons are sometimes vulnerable (Cossart et al., 2001).

Hilar SST neurons have been carefully studied anatomically. Besides SST, these neurons also express mGluR1 and substance P receptors (Freund and Buzsaki, 1996), and about 30% co-express neuropeptide Y (Chan-Palay, 1987). CST, that interacts with SST receptors, is not robustly expressed in hilus in young adult rodents (de Lecea et al., 1996), however in immature and aged rodents its expression is more robust (de Lecea et al., 1997; Winsky-Sommerer et al., 2004). SST interneurons represent about 16% of the total GAD-expressing (GABAergic) neurons in the dentate region (Kosaka et al., 1988), and have axons that terminate on the distal

dendrites of granule cells in the outer molecular layer, accounting for the thick plexus of SST immunoreactivity in this region in humans and rats (Amaral et al., 1988; Austin and Buckmaster, 2004; Csaba et al., 2005; Leranth et al., 1990; Milner and Bacon, 1989). Interestingly, SST terminals on granule cell dendrites are often closely apposed by SST-negative asymmetric (excitatory terminals), presumably perforant path synapes (Leranth et al., 1990; Milner and Bacon, 1989). Thus, SST neurons are poised to modulate input from entorhinal cortex, suggesting they may be key regulators of excitatory input into hippocampus. An axonal plexus that remains within the hilus has also been observed, suggesting SSTergic interneurons may also be involved in local modulation of hilar neurons. (Leranth et al., 1990; Lubke et al., 1998). SST-positive dendrites are spiny and appear to remain in the hilus. They likely receive input from mossy fiber collaterals of dentate granule cells (Freund and Buzsaki, 1996).

Although the above anatomical findings suggest a role for these neurons in feedback inhibition of dentate granule cells, the functional consequence the seizure-induced death of SST/GABAergic interneurons is still unclear. A major question is how or whether the death of these interneurons contributes to seizure-induced epileptogenesis. Several studies from human tissue (Colder et al., 1996; Isokawa-Akesson et al., 1989; Uruno et al., 1995; Wilson et al., 1998) and in animal models (Buckmaster and Dudek, 1997; Buckmaster and Dudek, 1997) have failed to find a decrease in feedback inhibition or any GABAergic inhibition in dentate granule cells after the seizure-induced death of these SST interneurons, indeed increased inhibition has even been reported (Buckmaster and Dudek, 1997; Haas et al., 1996; Tuff et al., 1983). However, a recent rigorous analysis of inhibition in dentate granule cells after pilocarpine-induced status epilepticus revealed some interesting changes. Following the death of SST interneurons, evoked monosynaptic inhibitory postsynaptic potentials (representing the postsynaptic response to released GABA) were reduced by about 40%. Furthermore, spontaneous and miniature inhibitory postsynaptic currents were decreased, indicating decreased GABA release (Kobayashi and Buckmaster, 2003). Similar finding were reported following electrically stimulated status epilepticus (Sun et al., 2007). These results suggest that careful analysis of GABAergic inhibition following the seizure-induced death of SST interneurons shows functional deficits that could have been missed in previous studies.

Beyond the impact on GABA function, another question that has not been nearly as well-studied is what is the consequence of the loss of SST function in the dentate by the death of SST-containing interneurons? To understand this, we must first understand the role of SST in “normal” dentate gyrus. Recordings from mouse hippocampal slices showed that, unlike in CA1 and CA3 pyramidal neurons (see below), exogenously applied SST does not have any notable effects on postsynaptic currents or firing properties of dentate granule cells. We also did not detect any effect of SST on synaptic responses recorded in the outer molecular layer and evoked by stimulation of perforant path input. However, we found that SST is a robust modulator of synaptic plasticity at lateral perforant path synapses. The presence of nM concentrations of SST prevents the generation of long-term potentiation (LTP) by high frequency trains of stimulation (Baratta et al., 2002). This form of synaptic plasticity is critical for some types of learning and memory, and is also thought to play a role in epileptogenesis (Sutula and Steward, 1986; Sutula and Steward, 1987; Wasterlain et al., 1999). The major mechanism by which SST appears to act is postsynaptic inhibition of N-type Ca^{2+} channels, which participate in depolarizing the dendrites sufficiently to induce LTP (Baratta et al., 2002). We also showed that endogenously released CST can depress LTP at this synapse. In a mouse in which CST was transgenically expressed in dentate, no LTP at lateral perforant path synapses could be generated either in vivo or in vitro. Interestingly, this mouse also showed major deficits in hippocampal-dependent learning (Tallent et al., 2005).

The actions of SST in hippocampus following seizure-induced alterations have not been studied. The majority of SST receptors in the dentate are localized on dentate granule cells, which are resistant to seizure-induced death. Thus, SST receptors in the dentate are largely spared following seizure-induced neuronal death (Perez et al., 1995). However, possible downregulation of SST_2 receptors in dentate following seizures has been reported. SST_2 immunoreactivity is decreased in the outer molecular layer but not CA1 or CA3 hippocampal regions following kindling-induced seizures (Csaba et al., 2004). Another study showed a decrease in SST binding in the outer molecular layer after kindling that was not associated with any changes in SST receptor mRNA levels (Piwko et al., 1996). Further evidence for SST_2 receptor down-regulation comes from studies in hippocampal tissue resected from humans during surgery for intractable seizures (Csaba et al., 2005). In hippocampus from patients with temporal lobe epilepsy, SST_2 immunoreactivity and mRNA is decreased in CA1 and CA3 regions, likely reflecting neuronal loss. In dentate gyrus, SST_2 mRNA was strongly upregulated, and SST_2 binding was increased in the inner molecular layer but robustly decreased in the outer molecular layer. These results were interpreted as reflecting downregulation of the receptor by seizure-induced SST release (see below).

The reason that this population of interneurons is selectively vulnerable to seizure-induced death is unclear. One possibility is that these neurons are “doubly stimulated” by both perforant path input from the cortex and mossy fiber input from the dentate granule cells, leading to excitoxicity. This hypothesis is based on an early electron microscopy study that detected SST-positive dendrites in the outer molecular layer closely apposed by putative perforant path terminals (Leranth et al., 1990). However, the majority of anatomical data suggests most SSTergic dendrites stay within the hilus, and that their main excitatory input comes from mossy fibers of dentate granule cells (Freund and Buzsaki, 1996). This is supported by studies looking at activation of dentate neurons following seizures using expression of the activity-dependent transcription factor *cfos* as a marker. These studies suggest that SSTergic interneurons neurons are activated *after* dentate granule cells (Le Gal La Salle, 1988; Peng and Houser, 2005), whereas one would suspect if they received direct input from perforant path they would be activated simultaneously.

Another reason suggested for their vulnerability to excitotoxicty is the complement of Ca2+ binding proteins that neurons express. Unlike in CA1 or CA3, SST containing interneurons in the hilus do not contain parvalbumin, calretinin, or calbindin (Bouilleret et al., 2000). This could leave hilar SST neurons particularly vulnerable to Ca^{2+}-induced excitotoxicity. A recent study in Ca^{2+} binding protein knockout mice suggests they play a role. In mice with both parvalbumin and calbindin knocked out a dramatic increase in vulnerability of SST-containing interneurons to kainate was observed. In the double knockout, only 12% and 6% of the CA1 SST-containing neurons remained one and 30 days after kainate injection, respectively, compared to 43% and 29% in wild type mice. In mice with both parvalbumin and calretinin knocked out, a larger decrease in CA1 SST immunoreactivity was observed 30 days but not one day following kainate injections (Bouilleret et al., 2000). This study suggests that knockout of calbindin in particular leads to increased susceptibility of SST interneurons to seizure-induced death. Thus, the lack of Ca^{2+} binding proteins in hilar SST interneurons could contribute to their vulnerability to seizures and other insults.

Another recent study points to a signaling cascade impacting the vulnerability of hilar SST neurons to seizure-induced death (Choi et al., 2007). Activation of the MAP kinase ERK1/2 has been shown to be neuroprotective (Hetman et al., 1999). SST neurons in the hilus contain high levels of the striatal-enriched protein tyrosine phosphatase (STEP). This protein acts as a negative regulator of ERK1/2 activity. Systemic injection of the STEP inhibitor FK506 15 min *after* induction of seizures with pilocarpine conferred long-lasting protection (7 days) on hilar SST neurons. Furthermore, injection of the inhibitor was associated with an increase in

phospho-ERK expression in hilar SST neurons, suggesting activation of ERK1/2. These observations, although intriguing, do not fully explain the differences in vulnerabililty of hilar SST neurons to seizure-induced death, since seizure-resistant SST neurons in CA1 also express STEP (Choi et al., 2007).

SST release and expression is upregulated by seizures

The SST gene contains a prototypical CRE (cAMP regulatory element) site that confers activity-dependence (Montminy and Bilezikjian, 1987). Therefore, prior to the death of SST-containing neurons, or in models such as kindling where SST neurons are less vulnerable, SST expression is increased by seizures (Hashimoto and Obata, 1991). SST mRNA expression and immunoreactivity are remarkably enhanced in the soma of interneurons in the hilus and stratum oriens of CA1 and CA3, and their projections in outer molecular layer and stratum lacunosum moleculare one day to one month after hippocampal kindling (Schwarzer et al., 1996; Wanscher et al., 1990). Interestingly, ectopic expressing of SST in dentate granule cells has also been demonstrated after seizures (Calbet et al., 1999; Hashimoto and Obata, 1991).

SST release following seizures is robust, not surprising considering the frequency-dependent nature of neuropeptide release (for review, see (Baraban and Tallent, 2004)). SST release in hippocampus is enhanced 48 min following a seizure, with increased release continuing for the 3 hr recording period after the seizure (Manfridi et al., 1991). Baseline and K+ -induced SST release was significantly higher in hippocampal slices kindled rats vs. control rats (Vezzani et al., 1992). An in vivo study microdialysis study reported similar findings, i.e., an increase in both basal and K+ -stimulated release in hippocampus after kindling (Marti et al., 2000). Increased SST release following seizures would likely be protective (see below).

The change of SST expression and release could be significant in controlling excitatory neurotransmission in the hippocampus. Granule cells in the molecular layer send excitatory projections to pyramidal neurons in the CA3, the “pacemaker” of seizures in hippocampus. The afferent projections of SST- containing interneurons in the hilus inhibit granule cells (Leranth et al., 1990; Milner and Bacon, 1989). These interneurons are also heavily innervated by mossy fiber collaterals of granule cells. These findings indicate that SST-containing interneurons in hippocampus are activated by repeated seizures with brief durations and limited intensity. Therefore, this circuitry would provide feedback inhibitory control on granule cells.

Effect of exogenous SST on seizure using in vivo models

Vezzani et al. showed that intrahippocampal infusion of octreotide, an SST_2 agonist significantly reduced the total number and duration of seizures in rats (Perez et al., 1995; Vezzani et al., 1991). Mazarati and Telegdy (Mazarati and Telegdy, 1992) did a comprehensive study to determine the action of SST on seizures and in which brain regions it exerted its antiepileptic actions. They found that SST administered into cerebral ventricles, hippocampus or amygdala could significantly reduce the seizure severity. Secondly, infusion of anti-SST serum into the hippocampus had a proepileptic effect and blocked antiepileptic effects of SST administered intracerebroventrically. However, infusion of anti-SST serum into amygdala did not have proepileptic effects and did not block antiepileptic effects of SST. Another study demonstrated that continuous infusion of a SST-antibody into the hippocampus significantly accelerated seizure kindling, as suggested by a 40% reduction of stimulation needed to reach tonic and clonic seizures (Monno et al., 1993). These results suggest endogenous SST plays an important role in maintaining a seizure-free state and that the hippocampus is the critical site of action.

SST inhibition of epileptiform activity in hippocampal slices

Studies in hippocampal slices have shown that interictal or “between seizure” bursts are generated in CA3 (Traub and Wong, 1983; Wong and Traub, 1983) and transmitted to CA1 synaptically, where they can sometimes transition to ictal or seizure events (Traynelis and Dingledine, 1988). Thus both CA1 and CA3 are critical for generation of hippocampal electrographic seizure activity. We used the rat hippocampal slice preparation to further characterize the antiepileptic actions of SST in these regions of hippocampus. SST inhibits evoked and spontaneous epileptiform bursting in CA1 using two distinct models, the low Mg^{2+} model in which the excitatory drive is increased by removal of Mg^{2+} block on NMDA receptors, and addition of bicuculline that decreases inhibitory drive by blocking $GABA_A$ receptors (Tallent and Siggins, 1999). SST has been shown to have several distinct inhibitory actions at the cellular level in rat CA1 pyramidal neurons. SST increases two different types of K^+ currents, the voltage-sensitive M-current (Moore et al., 1988; Schweitzer et al., 1990) and a voltage-insensitive leak current (Schweitzer et al., 1998). By acting on these two currents, SST has hyperpolarizing effects across a wide range of voltages. SST also reduces excitatory synaptic input at Schaeffer collateral synapses from CA3. We showed that SST reduced excitatory postsynaptic currents evoked by stimulating Schaeffer collaterals (Tallent and Siggins, 1997). This effect is likely due to presynaptic inhibition of glutamate release by SST (Boehm and Betz, 1997). Thus SST has synergistic pre- and postsynaptic actions that reduce CA1 pyramidal cell excitability.

SST also reduces epileptiform events in the CA3 region of hippocampus (Tallent and Siggins, 1999). SST acts specifically on the synapses that generate spontaneous epileptiform activity in this region, the associational/commissural synapses that form a dense network of recurrent interconnections between CA3 neurons. EPSCs generated at mossy fiber synapses, that are the input from dentate granule cells, are insensitive to SST (Tallent and Siggins, 1999). Postsynaptic hyperpolarization of CA3 pyramidal neurons by SST has also been reported, although characterization of the underlying conductances was not performed (Tallent and Siggins, 1999). We also showed in this study using local application of SST that the peptide can act independently in CA1 and CA3, but has the most robust actions when working in both regions.

Since a major postsynaptic effector for SST receptors is augmentation of the K^+ M-current (I_M), this is a likely mechanism contributing to the antiepileptic actions of SST. Direct activation of I_M by retigabine has antiepileptic effects in vivo and in vitro (Qiu et al.,; Qiu et al., 2007; Rundfeldt, 1997; Rundfeldt and Netzer, 2000), and this drug is now in Phase III clinical trials for treating partial seizures (Porter et al., 2007). I_M has a critical role in preventing the generation of seizures in hippocampus. We recently showed that blocking I_M can convert interictal bursts to ictal bursts in both CA1 and CA3 hippocampus, and likewise, augmenting I_M with retigabine converts ictal bursting to interictal (Qiu et al., 2007). This effect is especially strong in immature hippocampus. We used hippocampal slices to examine the effects of SST on spontaneous bursting in CA1 and CA3 induced by low Mg^{2+} and with I_M blocked with the selective antagonist linopirdine. We found that SST inhibition of bursting in CA3 was not compromised, however, its ability to inhibit CA1 bursting was reduced (Figure 1). We compared these effects to another neuropeptide, Noc/OFQ, that has been shown to increase I_M in both CA1 (Madamba et al., 1999) and CA3 (Tallent et al., 2001). We had previously shown that a maximal concentration of Noc/OFQ was able to fully inhibit CA3 epileptiform bursting in the presence of linopirdine (Tallent et al., 2001). We found similar results using a submaximal (100 nM) concentration of Noc/OFQ in both CA3 and CA1 (Fig. 1). These results suggest that SST augmentation of I_M in CA1 is critical for its antiepileptic action, but other mechanisms are more important in CA3. The most likely candidate pathway is presynaptic inhibition of glutamate release at associational/commissural synapse (Tallent and Siggins,

1999), as these synapses are critical for generation of epileptiform bursting (Wong and Traub, 1983). Interestingly, augmentation of I_M by Noc/OFQ, the cognate receptor of which is closely related to the SST receptor family (Anton et al., 1996), does not appear to be necessary for its antiepileptic actions in the hippocampal slice, even though it robustly couples to this current (Tallent et al., 2001).

Is the somatostatin system an appropriate target for antiepileptic drugs?

The rationale for utilizing SST-related targets for treating intractable temporal lobe seizures appears strong. This is based on the fact that 1) The SST system is clearly compromised in post-seizure hippocampus, suggesting a deficit could contribute to both epileptogenesis and seizures, and 2) in animal models SST has robust antiepileptic activity both in vivo and in vitro. Interestingly, clinical trials are planned to use viral-vector mediated transfection of two other inhibitory neuropeptides, neuropeptide Y and galanin, to treat refractory partial seizures. This has been demonstrated to be an effective strategy in animal models (Lin et al., 2003; Richichi et al., 2004).

However, several caveats on use of SST-related targets in treatment of epilepsy must be considered (many of these caveats would apply to other neuropeptide systems as well). A major consideration would be a concern with disruption of endogenous SST effects. SST is widely distributed in the brain, although its role in most brain regions is unclear. However, this peptide clearly plays a role in cognition (Baraban and Tallent, 2004; Tallent et al., 2005), food intake (Stepanyan et al., 2007), fear conditioning (Fendt et al., 1996), and hormone regulation (i.e., growth hormone) (Brazeau et al., 1972). Thus targeting a SST receptor that is widely distributed (e.g., SST_2, that appears to be the major receptor in most brain regions) would likely disrupt the normal physiological function of SST. Unfortunately, SST_2 is indeed the receptor that appears to mediate the majority of the antiepileptic effects of SST, at least in rats (Perez et al., 1995; Vezzani et al., 1991), although this same group showed SST_2 did not contribute significantly in mice (Moneta et al., 2002). Our studies in mice demonstrate that SST_4 may be the critical receptor in mediating the antiepileptic effects of SST (Qiu et al., 2005). This receptor has much more limited distribution than SST_2, making it a more advantageous drug target. However, it is unknown which SST receptor is more critical in humans, or, for that matter, whether SST has antiepileptic actions in humans. Studies in human hippocampus resected during epilepsy surgery, as has been done for neuropeptide Y (Patrylo et al., 1999), are critical for validating SST receptors as valid antiepileptic targets.

Another major issue is receptor desensitization. SST_2 for example, is very sensitive to downregulation, even by endogenously released SST (Dournaud et al., 1998). Seizures, which lead to release of large amounts of SST, result in sustained loss of surface expression of SST_2 in the dentate gyrus (Csaba et al., 2004). However, some synthetic neuropeptide agonists have much less action on receptor internalization that the native peptide (Whistler et al., 1999), including some for SST (Engstrom et al., 2005; Koenig et al., 1997; Liu et al., 2005). Thus it may be possible to design an appropriately-selective SST agonist with a low propensity for receptor downregulation.

Conclusions

The specific loss of SST-containing interneurons in the hilus of the dentate gyrus is a hallmark of epileptic hippocampus. How this neuronal loss contributes to epileptogenesis or post-seizure hyperexcitability is unknown. However, in vivo and in vitro studies show that SST has strong inhibitory effects in hippocampus, indicating this neuropeptide is an important negative regulator of limbic excitability. SST_2 and SST_4 receptors are the most likely mediators of SST antiepileptic effects. The high number of patients with refractory temporal lobe seizures, and

the limited number of proteins on which the currently available antiepileptic drugs act suggests validation of new targets is critical. Therefore there is a need to examine the actions of agonists at SST_2 and SST_4 in hippocampus at both the cellular and in vivo level, and to validate the actions of SST and selective agonists in human hippocampus.

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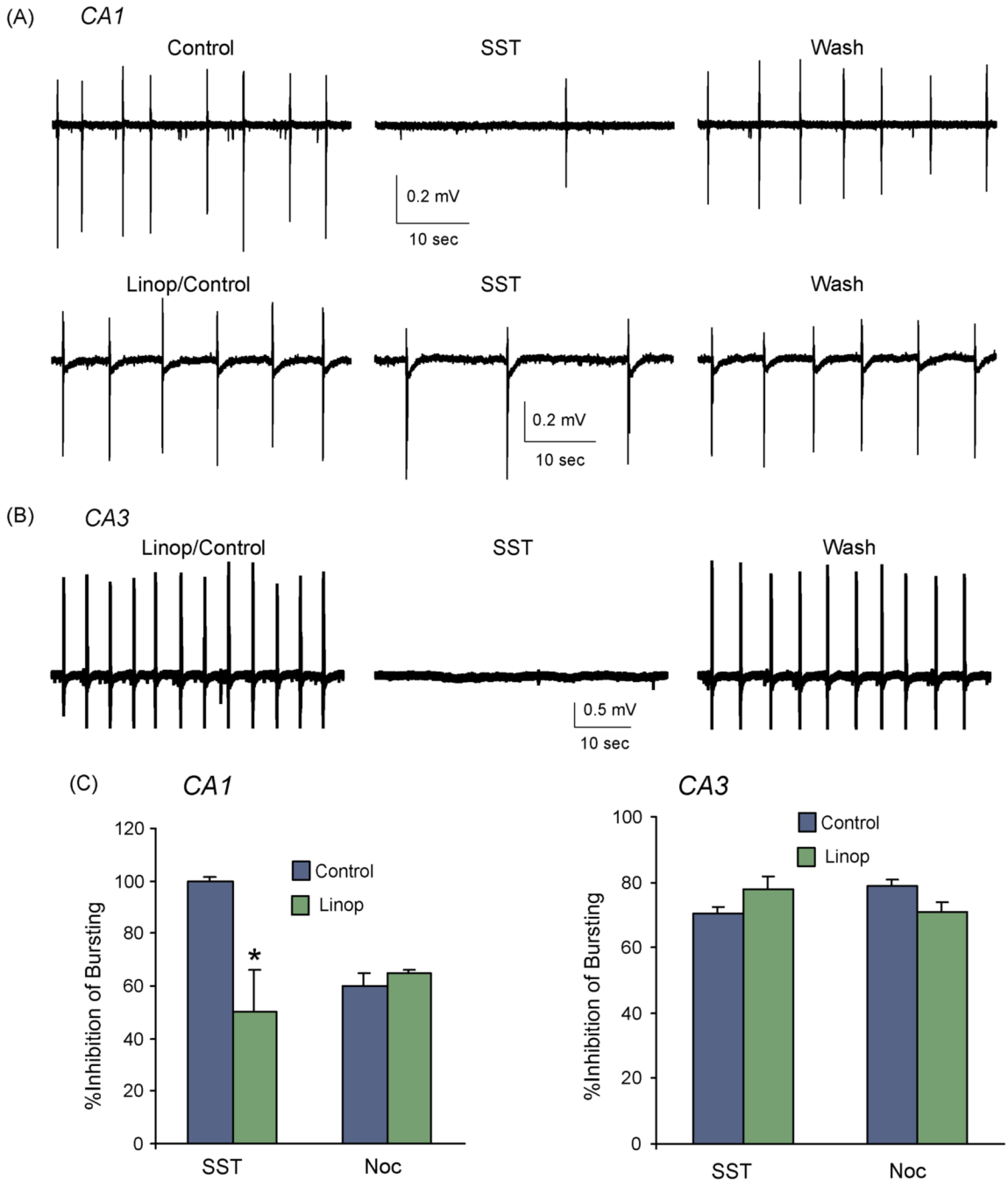

Figure 1.

Role of M-current in antiepileptic actions of somatostatin (SST) and Noc/OFQ in rat hippocampal slices. **A.** In Mg^{2+}-free ACSF, SST robustly inhibits bursting in CA1. Average interevent interval was 5.2 sec before and 31.9 sec after addition of 1 μM SST. In a different slice, 10 μM linopirdine (linop) was added 30 min prior to addition of SST. In this slice, SST increases the interevent interval in CA1 from 7.2 to 15.6 sec. **B.** Shown is an example where SST completely blocks CA3 bursting in linopirdine, suggesting M-current is not involved in SST inhibition in this region. **C.** Mean data for neuropeptide effects with and without linopirdine. SST, 1 μM, Noc, 0.1 μM. Only SST inhibition in CA1 is significantly reduced in the presence of linopirdine (indicated by *, $p < 0.05$, unpaired t-test). N = 4 for all conditions.