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ORIGINAL INVESTIGATION

Anxiolytic and antidepressant actions of somatostatin: the role of sst2 and sst3 receptors

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Abstract
Rationale and objectives Somatostatin is a cyclic polypeptide that inhibits the release of a variety of regulatory hormones (e.g., growth hormone, insulin, glucagon, and thyrotropin). Somatostatin is also widely distributed within the central nervous system (CNS), acting both as a neurotransmitter and as a neuromodulator. Recently, we showed that intracerebroventricular (i.c.v.) administration of somatostatin reduced anxiety-like and depression-like behaviors in animal models. The somatostatin receptor subtypes that are involved in these behavioral effects, however, have not been investigated. In the CNS, the neurotransmitter actions of somatostatin are mediated through five G-protein coupled receptors (sst1 to sst5).
Materials and methods We examined the behavioral effects of i.c.v. microinfusions of different doses of selective agonists of each of the five somatostatin receptor subtypes. Their behavioral effects were assessed in the elevated plus-maze and the forced swim apparatus, rodent models of anxiolytic and antidepressant drug effects, respectively.
Results Anxiety-like behavior was reduced following i.c.v. infusions of a selective sst2 receptor agonist, but not after infusions of the other four receptor agonists. An antidepressant-like effect was observed following infusions of either sst2 or sst3 agonists.
Conclusions The results add to our nascent understanding of the role of somatostatin in anxiety- and depression-like behavior and suggest a clinical role for somatostatin agonists for the simultaneous treatment of anxiety and depression, which are often comorbid.

Keywords Somatostatin · Anxiety · Depression · Agonist · Plus-maze · Swim test

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Introduction

Somatostatin (somatotropin release inhibiting factor; Brazeau et al. 1973) is a cyclic polypeptide with two biologically active isoforms (SST-14 and SST-28) arising from the same pro-hormone. Somatostatin regulates the release of several hormones in the gastro-intestinal tract and pancreas (e.g., insulin and glucagon), and modulates smooth muscle contractility and cell proliferation (Weckbecker et al. 2003). Somatostatin is also widely distributed within the central nervous system (CNS), acting both as a neurotransmitter and a modulator of other neurotransmitter systems (Meyer et al. 1989; Chesselet and Reisine 1983).

Five G-protein coupled receptors (sst1-5) mediate the neurotransmitter actions of somatostatin in the brain, with the sst1 receptor acting primarily as an autoreceptor (Roosterman et al. 1999; Thermos et al. 2006). The sst2 receptor is found as two splice variants, $sst2_A$ and $sst2_B$, which differ only in length and composition of their respective carboxyl-terminal domains. Both variants are expressed in the brain, though in different densities across brain areas (Schindler et al. 1999; Yamada et al. 1992).

While the sst2 receptor is the most abundant form in the brain, all five receptor subtypes are expressed here, and their distributions have been mapped using in situ hybridization and immunohistochemistry (Dournaud et al. 2000; Selmer et al. 2000). The effects of somatostatin

binding at its G-protein coupled receptors are generally inhibitory, either through increasing K^+ currents or through decreasing Ca^{2+} currents (Baraban and Tallent 2004; Cervia et al. 2008; Meis et al. 2005; Tallent and Siggins 1997). Somatostatin neurons are thought to play an important role in negative feedback circuits (Binaschi et al. 2003).

There is evidence that central somatostatin is involved in several processes, such as sleep architecture (Beranek et al. 1997; Danguir 1986; Frieboes et al. 1997; Hajdu et al. 2003; Obal et al. 2003; Steiger et al. 1992; Toppila et al. 2000; Ziegenbein et al. 2004), epileptiform activity (Binaschi et al. 2003; Buckmaster et al. 2002; Mazarati and Telegdy 1992; Moneta et al. 2002; Tallent and Qiu 2008; Tallent and Siggins 1999; Vezzani and Hoyer 1999), memory formation and retention (Dournaud et al. 1996; Dutar et al. 2002; Dyer and Cain 2007; Gastambide et al. 2009; Justino et al. 1997; Kluge et al. 2008; Lamirault et al. 2001; Low et al. 1998; Matsuoka et al. 1994, 1995; Nilsson et al. 1993; Tashev and Belcheva 2008; Tokita et al. 2005; Zeyda et al. 2001), locomotor activity (Hathway et al. 2004; Izquierdo-Claros et al. 2001; Marazioti et al. 2005, 2006, 2008; Raynor et al. 1993; Santis et al. 2009; Tashev et al. 2001, 2004), and nociception (Betoin et al. 1994; Carlton et al. 2001; Morton et al. 1989; Pinter et al. 2006; Schindler et al. 1998; Tashev et al. 2001).

There is also indirect evidence that somatostatin may be involved in emotional processes such as anxiety and depression (e.g., Viollet et al. 2000; Fendt et al. 1996; Gheorvassaki et al. 1992; Pallis et al. 2006, 2007, 2009; Zhang et al. 1999), although none of these studies has directly stimulated somatostatin function in the brain and documented the outcome in pharmacologically validated animal models of anxiety or depression (see general "Discussion"). Recently, we showed intracerebroventricular (i.c.v.) microinfusions of somatostatin produced clear, anxiolytic- and antidepressant-like effects in the elevated plus-maze model of anxiety and the forced swim model of depression (Engin et al. 2008). Specifically, rats infused with somatostatin increased their open-arm activity in the plus-maze and spent more time swimming in the swim test, compared to vehicle-infused controls. Moreover, i.c.v.-infused somatostatin reduced the frequency of reticularly evoked hippocampal theta rhythm in urethane-anesthetized rats, an effect common to all classes of anxiolytic drugs (McNaughton et al. 2007). While these findings point to an anxiolytic and antidepressant action of somatostatin, the somatostatin receptor subtypes that mediate these effects are unknown.

The purpose of the present study was to begin characterizing the somatostatin receptor subtypes involved in the anxiolytic and antidepressant-like effects we found after microinfusion of the endogenous agonist, somatostatin. Accordingly, five synthetic somatostatin agonists, each selective for one of the somatostatin receptor subtypes (sst1 through sst5), were administered i.c.v. to different groups of rats. The behavioral effects were evaluated in the elevated plus-maze and the forced swim test.

Materials and methods

Subjects

Subjects were 107 male Sprague-Dawley rats, weighing 170–230 g at the time of surgery. The rats were individually housed in polycarbonate cages and maintained on a 12:12 h light/dark cycle (lights on at 0600 hours) for the duration of the experiment. Food and water were available ad libitum. The treatment of all animals was in compliance with the National Institute of Health Guide for Care and Use of Laboratory Animals and the Canadian Council on Animal Care. The elevated plus-maze data for one animal that received an sst5 agonist infusion were eliminated because it fell off the maze more than two times. Data from the same animal, however, were used in the statistical analysis of behavior in the forced swim test.

Surgery

Rats were anesthetized with isoflurane (4% induction, 2% maintenance in 30% N_2O and 70% O_2), injected with atropine sulfate (0.1 mg/0.2 ml i.p.) and marcaine (1.5 mg/0.3 ml, s.c. on the head), placed in a stereotaxic frame (Kopf Instruments, Tujunga, CA, USA), and hydrated with 0.9% saline (3 cc, i.p.). An incision was made to expose the skull. The rats were implanted with stainless-steel 22-gauge guide cannulae (Plastics One, Roanoke, VA, USA) targeting the right lateral ventricle (AP: −0.8 mm, ML: −1.5 mm, DV: −3.5 mm). The cannulae were secured to the skull with three jeweler's screws and cranioplastic cement. A dummy cannula was inserted into each guide cannula in order to keep the cannula tract clear. The surgical wound was treated with 2.5 mg carprofen (Rimadyl©, Pfizer; 2.5 mg/0.5 ml s.c. on the head) at the end of the surgery. Following the surgery, the subjects were placed in a warm environment, until they regained consciousness. They were then allowed to recover for at least 6 days in their home cages before the start of behavioral testing. At the end of the experiments, rats were given an overdose of sodium pentobarbital, their brains extracted and sectioned, and cannula placements confirmed with infusions of a 2.5% Chicago blue solution (4 μl). All placements were within the lateral cerebral ventricles.

Infusion procedure

The sst1 agonist L-797591, sst2 agonist L-779976, sst3 agonist L-796778, sst4 agonist L-803087, and sst5 agonist

L-817818 were kindly provided by Merck Pharmaceuticals Research Laboratories, Rahway, NJ, USA. All drugs were dissolved in dimethyl sulfoxide (DMSO) at concentrations of 0.75, 2.25, and 6.75 μg/μl. Total infusion volume was kept constant at 4 μl per rat. Rats were randomly assigned to a DMSO control condition or to one of the drug conditions before the start of the experiment. DMSO has no known neurotoxic effects in the amounts administered in our experiments (Santos et al. 2003), and the behavioral patterns observed with DMSO are comparable to those observed with saline (e.g., Engin and Treit 2008a; Engin et al. 2008). L-797591, L-779976, and L-796778 were administered at doses of 3, 9, and 27 μg per rat. L-803087 and L-817818, however, caused seizure-like behavioral responses at the 27 and 9 μg doses, so that only the 3 μg dose of these two drugs could be tested. All compounds were administered via an infusion pump (Harvard Apparatus 22, MA, USA), at a rate of 4 μl/min, using a 26-gauge stainless-steel internal cannulae, attached by polyethylene tubing to a 10-μl Hamilton syringe. The internal infusion cannulae extended 0.5 mm below the ventral tip of the guide cannula. Drug flow was confirmed by displacement of a bubble inside the polyethylene tubing. The internal infusion cannula was left in place for 40 s after the end of the infusion period, to allow for diffusion.

Behavioral testing

All testing occurred in a quiet room between 0800 and 1600 hours. Testing started 20 min after the end of infusion period. The subjects received the same drug treatment or vehicle treatment for both behavioral tests. The plus-maze test occurred first, followed 6 days later by the forced swim test. This order of testing does not affect performance in swim test, although the reverse order can significantly affect plus-maze performance (see Korte and De Boer 2003; Walf and Frye 2008; Wu and Lin, 2008). There is no evidence of drug-carryover effects in our laboratory when several days separate the two tests (e.g., Menard and Treit 1998; Treit et al. 1993). All testing was recorded on videotape. The behavioral data were subsequently analyzed with analysis of variance and followed, where significant (α=0.05), with pairwise comparisons (least significant difference (LSD) post hoc tests, α=0.05).

Elevated plus-maze

The maze was a plus-shaped apparatus with an open roof, consisting of two 50×10 cm open arms, and two 50×10×50 cm enclosed arms, elevated at a height of 50 cm. Testing was conducted in a dimly illuminated (<15 lux) room. Each animal was tested for 5 min. Four variables were measured: (1) time spent in the open arms, (2) time spent in the closed arms, (3) number of entries into the open arms, and (4) number of entries into the closed arms. A rat was considered to have entered or spent time in an arm only when all four paws were in the respective arm. The time spent in the open arms and the number of open-arm entries were expressed as a percentage of total arm activity (open-arm time/(open-arm time+closed-arm time)×100), and total arm entries (open-arm entries/(open-arm entries+closed-arm entries)×100), respectively. A higher percentage of open-arm time or open-arm entries are taken as measures of anxiety-reduction (anxiolysis). In addition, the total of all arm entries (open-arm entries+closed-arm entries) and the total of closed-arm entries were used as indexes of general activity (Pellow 1986; Hogg 1996).

Forced swim test

The forced swim test occurred over 2 days, the first day by a 15-min 'pretest' swim session, followed on the second day by a 5-min 'test' swim session (Porsolt et al. 1978). The i.c.v. microinfusion was given once only, prior to the second 'test' session. Testing was done under normal light conditions. In both sessions, each animal was placed in a cylindrical plexiglass tank (46 cm high×20 cm in diameter) containing 30 cm of water. The water temperature was maintained at approximately 25°C. Three measures were taken during the test session: (1) the amount of time the animal spent swimming, (2) the amount of time the animal spent trying to escape (i.e., trying to climb to the walls of the tank), and (3) the amount of time the animal spent 'immobile' (i.e., floating in the water, making only the movements necessary to keep its head above water). Shorter immobility times (reduced behavioral "despair") is an effect characteristic of most antidepressant drugs, as well as non-pharmacological treatments for depression, such as electroconvulsive shock therapy (Willner 1994). After each session, the rats were immediately removed from the cylinder, dried with a towel, and kept under a heating lamp until completely dry before being returned to their home cages.

Results

Both the percentage of open-arm entries (F (11, 105)=2.98, p<0.01; Fig. 1a) and the percentage of open-arm time (F (11, 105)=2.30, p<0.02; Fig. 1b) were significantly different among the drug and control groups; whereas, the general activity measures did not differ across groups (Table 1; p>0.05).

An LSD post hoc test revealed that rats that received a 27-μg infusion of the sst2 agonist L-779976 made more entries into the open arms and spent more time in the open

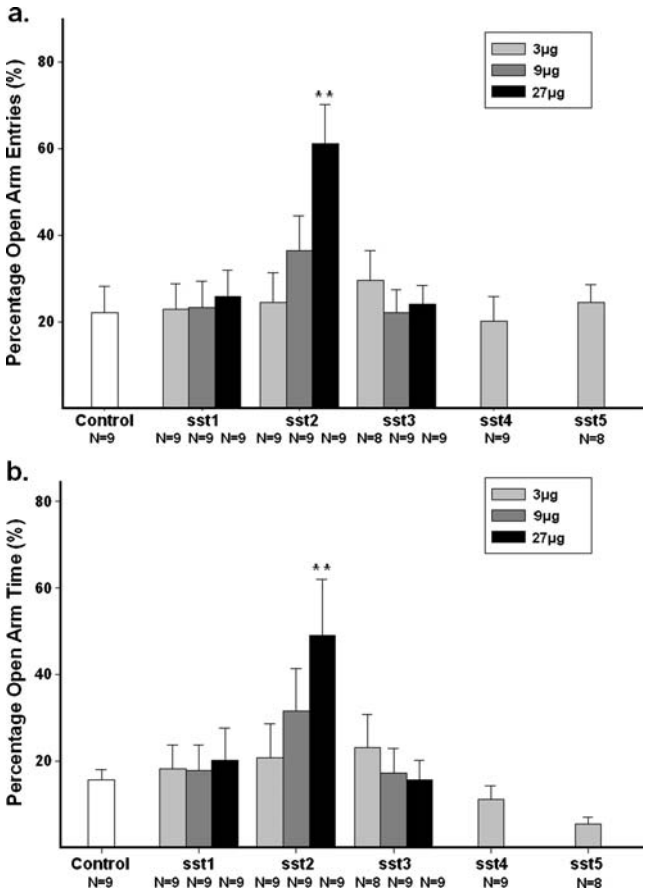

Fig. 1 Elevated plus-maze findings following i.c.v. administration of vehicle (dimethyl sulfoxide) or different doses of the five somatostatin agonists: **a** Mean (±SEM) percentage of open-arm entries. **b** Mean (±SEM) percentage of open-arm time. *Significantly different from the vehicle control group at $p<0.05$, **Significantly different from the vehicle control group at $p<0.01$ in a post hoc least significant difference test

arms than the DMSO controls (LSD, $p<0.01$). None of the other drug treatments produced significant changes in plus-maze behavior.

In the forced swim test, total mobility (F (11, 106)=1.87, $p<0.05$; Fig. 2a) was significantly increased by the 27-µg dose of the sst2 agonist L-779976 (LSD, $p<0.01$), as well as by the 27-µg dose of the sst3 agonist L-796778 (LSD, $p<0.02$). No other drug group was significantly different from the vehicle control group. In the case of the sst2 group (27 µg), the increase in mobility corresponded to an increase in swimming behavior (Fig. 2b; LSD, $p<0.01$); whereas for the sst3 group (27 µg), the increase in mobility was accompanied by an increase in both swimming (LSD, $p<0.05$) and climbing (LSD, $p<0.06$) behaviors (Fig. 2b, c).

Discussion

These findings taken together suggest that the anxiolytic-like effects of somatostatin we previously found were due to activation of sst2 receptors: While the administration of a selective sst2 agonist increased open-arm activity significantly above control levels, none of the other somatostatin receptor agonists displayed this effect. The increase in open-arm activity following sst2 agonist administration was comparable to that observed following administration of standard anxiolytic drugs (e.g., diazepam) in our laboratory and others (e.g., Engin et al. 2008; Engin and Treit 2008a; for reviews of methods and findings, see Treit 1985; Treit et al. 2003; Engin and Treit 2008b). On the other hand, the antidepressant-like effect of somatostatin seemed to involve both the sst2 and sst3 receptor subtypes, stimulation of which increased total mobility time in the forced swim test, an index of antidepressant drug action. The increase in mobility observed following sst2 and sst3 agonists was comparable to that observed following standard antidepressant drugs such as the selective serotonin reuptake inhibitor fluoxetine (e.g., Porsolt et al. 1991; Engin et al. 2009). In summary, the behavioral effects observed in the elevated plus-maze and forced swim tests following sst2 and/or sst3 agonists were equivalent to those of reference anxiolytic (i.e., diazepam) and antidepressant (i.e., fluoxetine) compounds, respectively.

Both the increase in open-arm activity in the plus-maze after i.c.v. infusion of the sst2 receptor agonist and the increased mobility in the swim test after i.c.v. infusion of the sst2 and the sst3 agonists are not readily explained by nonspecific changes in general activity. In the elevated plus-maze, none of these compounds significantly increased either measure of general activity (total arm entries or closed-arm entries) at any dose. This suggests that the changes produced by the sst2 and sst3 agonists were behaviorally selective.

Table 1 Activity measures from the elevated plus-maze following the i.c.v. administration of vehicle (DMSO) or different doses of the five somatostatin agonists: mean (±SEM) number of closed-arm entries and mean (±SEM) number of total arm entries

Drug	Dose (µg)	Closed-arm entries	Total arm entries
Vehicle	–	8.89±(1.29)	11.33±(1.31)
sst1	3	8.89±(1.21)	11.22±(1.32)
	9	9.00±(0.69)	12.56±(1.56)
	27	8.00±(0.85)	11.00±(0.91)
sst2	3	7.89±(1.17)	10.67±(1.51)
	9	7.11±(1.62)	10.56±(1.52)
	27	4.11±(1.14)	9.67±(1.31)
sst3	3	9.13±(1.23)	13.63±(2.01)
	9	8.78±(0.85)	11.22±(0.70)
	27	8.44±(1.43)	11.00±(1.61)
sst4	3	7.56±(1.12)	9.11±(1.05)
sst5	3	6.75±(0.96)	8.75±(1.03)

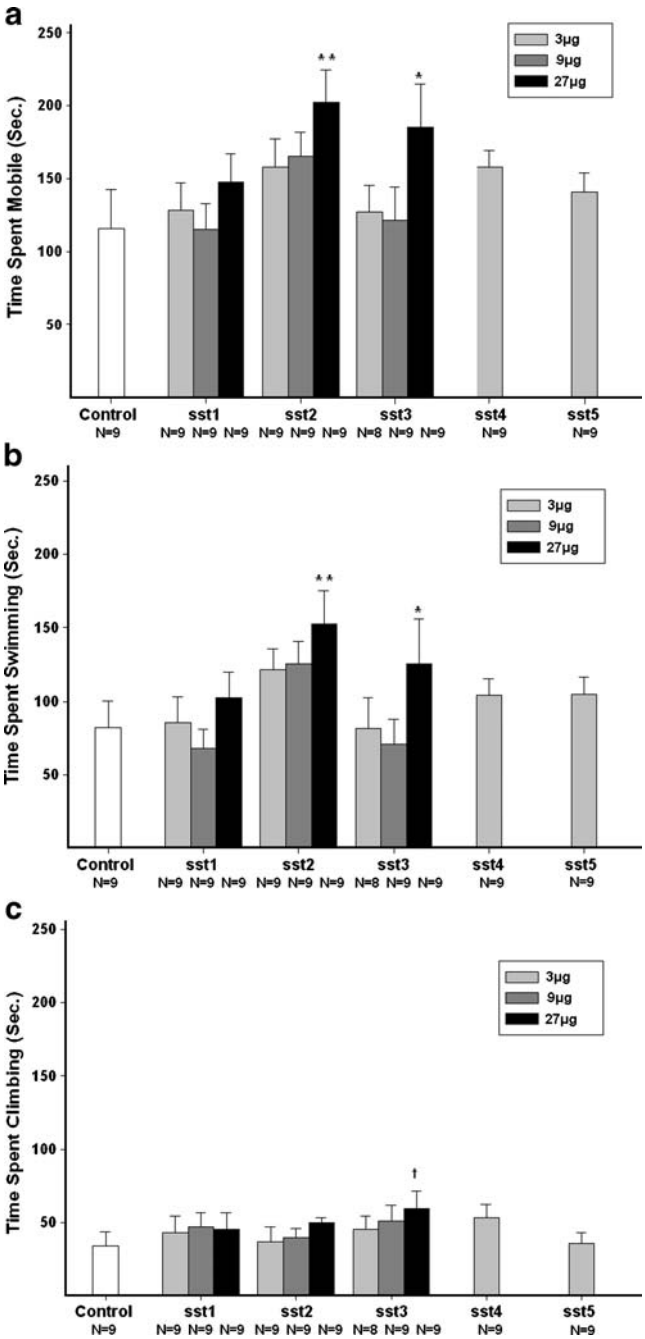

Fig. 2 Forced swim test findings following i.c.v. administration of vehicle (dimethyl sulfoxide) or different doses of the five somatostatin agonists: **a** Mean (±SEM) time spent immobile in seconds. **b** Mean (±SEM) time spent swimming in seconds. **c** Mean (±SEM) time spent climbing in seconds. †Significantly different from the vehicle control group at $p<0.06$, *Significantly different from the vehicle control group at $p<0.05$, **Significantly different from the vehicle control group at $p<0.01$ in a post hoc least significant difference test

The receptor specificity of the behavioral effects found in the present study, most of which appeared to be mediated by the sst2 receptor subtype, need to be confirmed by the reversal of these effects with somatostatin receptor antagonists. Be this as it may, the binding affinity of the sst2 agonist L-779976 for the sst2 receptor is 6,000 to 85,000-fold greater than its affinity for any other somatostatin receptor subtype (Rohrer et al. 1998). In comparison, the selectivity of the somatostatin antagonist, CYN154805, is far less (see van der Hoek et al. 2005). Although it is likely that somatostatin receptor antagonists will be developed that are more ideal for characterizing the receptor specificity of our agonist effects, we believe that the selectivity of sst2 agonist L-779976 is indicated—if not proven—by its high relative affinity for the sst2 receptor subtype and by its corresponding behavioral selectivity in animal models of anxiety and depression (present data).

Sst3 mRNA expression as well as immunohistochemical staining for the sst3 receptor itself indicates that it is widely distributed in the rat brain, most notably in the hippocampus and dentate gyrus, the amygdala, several hypothalamic nuclei, frontal and parietal cortices, the olfactory system, the cerebellum, and in brain stem nuclei such as locus coeruleus and raphe nuclei (Breder et al. 1992; Händel et al. 1999; Hervieu and Emson 1999; Kong et al. 1994; Perez et al. 1995. See Selmer et al. 2000 for a review and comparison to other sst receptor subtypes). Given the fairly broad distribution of sst3 receptors throughout the brain, it is not too surprising that they might play a role in behavior, and more specifically, a role in the antidepressant effects of somatostatin. However, the possibility remains that the sst3 receptor agonist used here actually produced its antidepressant-like effect by a nonspecific, partial activation of the sst2 receptor, which also produced antidepressant-like effects. While this possibility cannot be ruled out until a suitable antagonist study is conducted, it should be noted here that the binding affinity of L-796778 for the sst3 receptor is very high compared to its affinity for sst2 receptors (Ki in nanometer for sst3=24, for sst2>10,000). Combined with the very high relative affinity of the sst2 agonist used in this study, it seems more likely that the sst3 receptor agonist independently mediated at least some of the antidepressant-like effects reported here.

While our findings suggest that the sst2 and sst3 receptor agonists do not produce significant behavioral effects at doses below 27 µg, we were reluctant to test doses higher than 27 µg, because our sst4 and sst5 agonists appeared to produce seizures in some animals at doses of 27 and even 9 µg (non-systematic observations). This seizure-like activity seems counterintuitive considering that somatostatin itself has anticonvulsant-like actions (see Tallent and Qiu 2008 for a review). However, it should be noted that in rats, the anticonvulsant activity of somatostatin is mediated by sst2 receptors (Perez et al. 1995; Stragier et al. 2006; Vezzani et al. 1991; see Qiu et al. 2004, 2008 for different findings in mice). Moreover, the convulsive-like behavioral activity

observed in the current experiment did not show complete correspondence with typical epileptic-like convulsions observed in rats after electroconvulsant shock or pentylenetetrazole (e.g., Pinel et al. 1977). It is possible that in the case of the sst4 and sst5 receptor agonists, we observed tremors resulting from striatal dopamine release. Somatostatin is known to increase dopaminergic activity in the striatum (Hathway et al. 2004; Marazioti et al. 2008; Mitchell et al. 2000), although the specific receptors that mediate this effect are not known. In the case of sst4 agonists, it is also possible that the presynaptic facilitation of glutamate release caused by an activation of sst4 receptors resulted in seizure-like activity in the brain and the consequent convulsive-like behavior.

One of the remarkable aspects of somatostatin, in contrast to other anxiolytics, such as the benzodiazepines and other $GABA_A$ agonists, is that somatostatin has both anxiolytic and *pro*-cognitive effects (Engin et al. 2008). If both of these effects of somatostatin are specifically mediated by agonism of sst2 receptors, one might expect that the anxiolytic effect would be reversed by selective antagonism of the sst2 receptors, and that the pro-cognitive effects of somatostatin would also be reversed. While the first expectation has not yet been tested, previous studies have shown that antagonism of the sst2 receptor actually *facilitates* cognitive function (Dutar et al. 2002). Therefore, the specific activation of sst2 receptors may in fact have effects (anxiolysis and anterograde amnesia) similar to those of traditional $GABA_A$ anxiolytics (e.g., diazepam). Specific agonism of sst4 receptor function, on the other hand, results in an enhancement of at least some forms of memory function (Gastambide et al. 2009; Moneta et al. 2002). Thus, it is possible that the anxiolytic effects of somatostatin are mediated by sst2 receptors, while its pro-cognitive actions are mediated by sst4 receptors. Systematic studies involving the agonism and antagonism of specific somatostatin receptors need to be carried out to test these predictions, both in animal models of anxiety as well as models of learning and memory (e.g., McEown and Treit 2009).

The mechanism of the anxiolytic and antidepressant effects of sst2 receptor activation also needs experimental elaboration. Somatostatin has inhibitory effects in the brain (increased K+conductance, decreased Ca+ conductance), which are thought to be partly mediated by sst2 receptors (Jiang et al. 2003; Meis et al. 2005). The inhibitory role of somatostatin interneurons in limbic areas such as the hippocampus, the co-localization of somatostatin within GABAergic terminals in several brain areas (Esclapez and Houser 1995; Llorenscortes et al. 1992; McDonald and Mascagni 2002; Xie and Sastry 1992), and the inhibition of glutamate release following sst2 receptor activation (Baraban and Tallent 2004; Lanneau et al. 2000), could all contribute to the anxiolytic-like effects of somatostatin (see Engin and Treit 2008b). In addition, the dense distribution of sst2 receptors in anxiety-related structures such as the amygdala, the septum, the hippocampus, the hypothalamus, and the periaqueductal gray (Holloway et al. 1996) also supports a role for sst2 receptors in anxiety.

The antidepressant effect, on the other hand, may involve somatostatin's positive modulatory effects on serotonin release (Munozacedo et al. 1992; Popova et al. 1991). While the somatostatin receptor subtypes that mediate this facilitation of serotonin activity are unknown, the pattern of behavior we observed in the forced swim test following sst2 agonist administration may be informative. The sst2 agonist produced increased swimming behavior with no change in climbing behavior, a pattern that closely matches that observed following specific facilitation of serotonergic neurotransmission (Detke et al. 1995). Both the sst2 and sst3 receptor subtypes seemed to be involved in the antidepressant actions of somatostatin in our study, and it is noteworthy that these subtypes are expressed in the raphe nucleus and locus coeruleus (Selmer et al. 2000), the main sources of serotonergic and noradrenergic innervation of the forebrain, respectively. Thus, it is possible that the modulation of these monoamine systems by sst2 and sst3 receptors leads to the behavioral effects observed in the forced swim test. Experimental characterization of the interactions between the somatostatin, serotonin, and norepinephrine neurotransmitter systems may further contribute to, or refine, monoamine theories of depression.

Finally, it seems possible that somatostatin—or more likely one of its synthetic analogs—may ultimately represent a novel and effective treatment of both anxiety and depression. Somatostatin itself has a wide range of effects in both the CNS and the periphery, some of which may not be desirable. When combined with its relatively short plasma half-life and lack of receptor selectivity, somatostatin may be less attractive as a candidate for clinical use than its synthetic analogs (Pinter et al. 2006). However, while more stable analogs such as octreotide and lanreotide have been used in clinical settings to treat disorders such as inflammation, pain, tumor formation, and growth (Carlton et al. 2004; Chrubasik and Ziegler 1996; de Jong et al. 1999; Hofland et al. 1992; Pinter et al. 2006) and bind with high affinity to sst-2 receptors (Pinter et al. 2006), they do not show high receptor selectivity (Pawlikowski and Melen-Mucha 2003). Thus, these agents still do not resolve the issue of somatostatin's broad systemic and central actions. Nevertheless, it is reasonable to expect that further preclinical exploration will ultimately yield analogs with considerable receptor subtype selectivity. sst-2 receptor-specific agonists that are safe and have reasonably long half

lives may be particularly promising candidates for the clinical treatment of anxiety and depression, especially when these disorders are comorbid.

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