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Future clinical prospects in somatostatin/cortistatin/somatostatin receptor field

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Abstract

Somatostatin receptors (sst), somatostatin (SS) and cortistatin (CST) are widely expressed in the various systems in the human and rodent organisms and are "responsible" for maintaining homeostasis, which is essential for survival. Because of their broad expression pattern sst, SS and CST interactions may play regulatory roles in both physiology and pathophysiology in mammalian organisms. SS analogue treatment strategies as well as the use of SS analogues for diagnostic purposes have been established in diseases of different origins. This review focuses on the currently determined role for SS analogues in today's clinical practice and the potential clinical prospects for SS, CST and sst interactions in the future, with a focus on neuroendocrine and non-neuroendocrine tumours and immune-mediated diseases. Moreover, the role of new SS analogues and new insights in sst physiology will be discussed.

Keywords: Somatostatin; Cortistatin; Somatostatin receptor

1. Introduction

In mammals, proteolytic processing of a 116-amino acid prepro-SS results in the formation of two biologically active forms of SS, consisting of 14 and 28 amino acids, respectively (Patel and Galanopoulou, 1995). The amino acid residues Phe^7, Trp^8, Lys^9 and Thr^{10} are essential for binding of both SS isoforms to their five known receptors, $sst_{1–5}$ (Veber et al., 1979), which are G-protein coupled seven transmembrane receptors, having an N-terminal extracellular domain and C-terminal intracellular domain (Patel, 1999). Via binding to its receptors SS exerts its multiple effects, which are described extensively in the papers of the present journal. SS is widely expressed throughout the human body, like for instance in the central nervous system, gastro-intestinal tract and endocrine glands (Boehm and Betz, 1997; Chesselet et al., 1995; Lamberts, 1988; Reichlin, 1983a,b). In these tissues/systems SS exerts a mainly inhibitory role on secretion processes (Brazeau, 1986; Lamberts et al., 1996; Reichlin, 1983a). In addition, SS was also shown to have antiproliferative effects on different cell types in vitro.

Recently, the group of De Lecea and co-workers isolated a DNA clone encoding a novel neuropeptide from rat brain, called CST (De Lecea et al., 1996). Comparable to SS-14 and SS-28, proteolytic processing of procortistatin in rat results in the production of two isoforms, CST-14 and CST-29. The human peptide consists of 17 amino acids (De Lecea et al., 1997; Fukusumi et al., 1997). Because of its high structural resemblance to SS, CST binds with high affinity to the five known sst (Fukusumi et al., 1997). Recent studies have addressed the question whether CST is also more widely expressed than previously assumed, i.e. in the central nervous system. Wide expression of CST mRNA was detected in tissues throughout the human body (Dalm et al., 2004b). Moreover, a novel putative receptor has been described recently. This receptor, named MrgX2, has been shown to bind CST with highest affinity of over 2500 peptides evaluated, whereas SS only binds with low affinity to this receptor (Robas et al., 2003). These findings suggest that CST may act via either the sst or the MrgX2, which in term may explain some differences in effects between SS and CST. Our current knowledge on expression patterns of sst, SS and CST has opened a new area of research, in which the potential functional significance of these neuropeptides, apart from their known role in the brain, in different tissues throughout the human body is investigated.

The present review aims to give a brief overview of the potential (future) functional prospects of SS, CST and sst interactions

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in the various organ systems and discusses potential strategies for further research. We will focus on the potential clinical significance of SS and CST and their analogues in the fields of central nervous system abnormalities, endocrine actions, their place in oncology and immunology. Furthermore, the diagnostic and therapeutic significance of the development of new SS/CST analogues will be discussed.

2. Central actions in the SS/CST and sst network

2.1. Sleep regulation

De Lecea et al. (1996) identified for the first time the DNA clone encoding CST in rat cortex. Most of the actions of CST have been designated to the regulation of behaviour, sleep and memory mechanisms localized in the brain region. Compared to SS, CST shows both overlapping and differential effects on these various mechanisms. Both compounds seem to depress neuronal activity in the hippocampus (De Lecea et al., 1996), reduce development of seizures (Braun et al., 1998) and can deteriorate memory consolidation (Sanchez-Alavez et al., 2000). On the other hand, many differences in effects between SS and CST have been described. For example, CST-treated rats showed clear hypoactive behaviour and the electroencephalogram (EEG) showed a dramatic increase in cortical slow waves (De Lecea et al., 1996). Subsequently, after administration of CST, rats spent more time in slow-wave sleep and less time in Rapid Eye Movement (REM) sleep. On the other hand, the administration of SS results in sleep periods dominated by REM sleep, without significantly affecting the other phases of sleep (De Lecea et al., 1996; Feige et al., 1987; Fukusumi et al., 1997). Moreover, it has been demonstrated that CST expression is upregulated during sleep deprivation in rats. During sleep deprivation also upregulation of SS has been demonstrated in the brain (Toppila et al., 1997, 1996). This suggests that SS and CST both have sleep regulatory functions and probably interplay in the regulation of sleep, both in their own specific way. Previous studies demonstrated that acetylcholine (ACh) is present at low concentration in the cortex during slow-wave sleep, and higher concentrations of ACh are associated with wakefulness and REM sleep (Shiromani et al., 1987). Therefore, the question was addressed whether CST produces its sleep promoting effects by modulating ACh activity. It has been shown that CST antagonizes the effects of Ach (De Lecea et al., 1996), while SS is known to enhance the effects of ACh (Mancillas et al., 1986). Because of the distinct actions of SS and CST it was hypothesized that, instead of both peptides acting on the same sst, a specific receptor for CST might be responsible for the differences in the above mentioned effects (Calbet et al., 1999; Criado et al., 1999). With the detection of the more CST-specific receptor MrgX2 (Robas et al., 2003) and its expression in the brain region, an explanation for distinct actions between both peptides may be found. However, binding affinity of CST for the MrgX2 receptor is relatively low (Robas et al., 2003).

Summarizing, in behaviour en sleep regulation both SS and CST seems to play important regulatory roles, whereas the clinical significance of both peptides regulating these processes needs to be evaluated more extensively.

2.2. Epilepsy

Epilepsy is characterized by abnormal hyperexcitation, which can include several different brain regions. Temporal lobe epilepsy (TLE) involves the hippocampus (Sloviter, 1994). In tissues removed from patients with TLE a selective loss of SS containing neurons was found in the hilus of the dentate gyrus (De Lanerolle et al., 1989; Mathern et al., 1995). Comparable results were found in animal models for epilepsy (Mitchell et al., 1995; Sloviter, 1987) in which SS containing neuronal loss can extend beyond the hilus to the rest of the hippocampus (Lahtinen et al., 1993). Recent studies have investigated the pathways involved in SS neuron loss in epilepsy, and it seems that the extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK) pathway may be involved (Choi et al., 2007). The function of these SS neurons and the consequences of their loss are unknown. However, the majority of SS interneurons make inhibitory synapses onto primary hippocampal neurons (Freund and Buzsaki, 1996; Leranth et al., 1990), suggesting their involvement in inhibitory processes. The loss of SS neurons in early stages of epilepsy may contribute to subsequent abnormal hippocampal hyperexcitability (Freund and Buzsaki, 1996; Leranth et al., 1990).

Intracerebroventricular and intrahippocampal injections of SS and SS analogues have been shown to modulate seizure activity in animal models. Early studies suggested that SS had a stimulatory effect on seizures (Higuchi et al., 1983; Perlin et al., 1987), however, more recent studies, in which SS was directly injected into the hippocampus, have demonstrated inhibitory effects on electrical seizures recorded in vivo (Vezzani et al., 2000, 1991). Moreover, administration of SS to hippocampal CA1 and CA3 pyramidal neurons reduces epileptiform events in hippocampal slices (Tallent and Siggins, 1999) and SS knockout mice show an increase in severity of seizures induced by kainate, a glutamate receptor analogue (Buckmaster et al., 2002). In rat brain sst_2 selective agonists have been shown to decrease seizure severity (Vezzani and Hoyer, 1999). These findings in animal models both in vitro and in vivo show an important role for SS in regulating seizure activities. The exact mechanisms remain to be determined in future studies in transgenic and knock-out mice which allows for temporally and regionally controlled expression and deletion (Baraban and Tallent, 2004). The potential clinical significance of SS or its analogues with respect to therapeutical options in epilepsy therefore seems to be still far ahead.

3. Neuroendocrine disorders

SS was initially identified as an growth hormone release inhibiting factor (Brazeau et al., 1973) from the ovine hypothalamus. SS in animals and human, however, was found to exert broader inhibitory effects on hormone secretion, like insulin and glucagon. These inhibitory effects have formed the basis for the application of SS analogues in treatment of endocrine