Somatostatin receptors in the brain

ABSTRACT

Somatostatin is a peptide that participates in numerous biochemical and signaling pathways. It functions *via* receptors (SSTRs1-5), which belong to the family of receptors coupled with protein G. All somatostatin receptors are characterized by a certain degree of homology in molecular structure. The cell effects of their agonists in peripheral tissues rely mainly on the inhibition of the hormones release. Somatostatin is also an important neuromodulator and neurotransmitter. SSTRs may affect other receptors, forming structural and functional homodimers and heterodimers. SSTRs play also role in the regulation of physiological processes, such as itching and pain, reproductive functions, regulation of feeding or mood. Besides physiological functions, SSTRs contribute also to the pathogenesis of glial tumors, neurodegenerative diseases, or post hemorrhagic stroke changes. Recent years of research have provided new data regarding the role of somatostatin receptor signaling pathways in the brain and the knowledge in this field is developing rapidly.

INTRODUCTION

The history of the somatostatin discovery goes back to the 1970s, when scientists conducted research on a peptide synthesized in the hypothalamus, which acts as the inhibitor of the pituitary growth hormone – somatotropin release. The name somatostatin (SST) was proposed first time by Paul Brazeau in the journal Science in 1973. Previously, the term "somatotropin-release inhibiting factor" (SRIF) was used [1]. Shortly after the publication of this paper, researchers from California described the primary structure of somatostatin isolated from the sheep hypothalamus [2]. Subsequent years of research have shown that SST is involved in the modulation of central nervous system activity and may affect processes such as locomotor activity and sleep. Administration of relatively high doses of somatostatin directly to the brain resulted in disturbances of the sleep-wake cycle in rats, as well as catatonia, paralysis and tonic-clonic seizures [3-4].

Six somatostatin peptides (described SS1-6), encoded by separate genes, have been described in vertebrates so far [5]. Among them there are two bioactive isoforms: SS14, composed of 14 amino acids and SS28, composed of 28 amino acids. Both forms act through the same receptors, however the shorter isoform SS14 primarily causes biological effects in the nervous system, whereas the longer SS28 is more reactive to receptors expressed in the pancreas and is responsible mainly for endocrine effects of this organ [6]; although it activates receptors located in the retina and the brain as well [7]. On the periphery somatostatin is released by delta cells present on the pyloric antrum, the duodenum and the pancreatic islets and in the brain by neuroendocrine neurons of the ventromedial nucleus of the hypothalamus.

Somatostatin plays an important role in the regulation of vertebrate development, growth and metabolism [8-10]. The systemic function of this peptide is inhibition of the release of growth hormone, insulin, glucagon, gastrin, secretin and cholecystokinin [11-13]. Five somatostatin receptors (SSTR1-5) [14] have been characterized in mammals, and six receptors in fishes (SSTR1-3, SSTR5-7) [8,15,16]. Binding of somatostatin to each of the receptor subtypes results in inhibition of adenylate cyclase (AC) in vertebrates [17]. All somatostatin receptors described so far are expressed in the brain and in many peripheral tissues, which was confirmed by studies determining the mRNA and protein level [8,14,15]. SSTRs belong to the super-family of G-protein coupled receptors (GPCR), which is the largest family of transmembrane cell-surface signaling proteins that play a key role in the major signaling pathways associated with metabolism, normal cell differentiation and neurotransmission.

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Abbreviations: AC – adenylyl cyclase; AD – Alzheimer disease; CB1R – cannabinoid receptor type 1; D2R – dopamine receptor D2; GEP-NEN – gastroenteropancreatic neuroendocrine neoplasms; GnRH – gonadotropin-releasing hormone; GPCR – G Protein-Coupled Receptor; MAPK – mitogen-activated protein kinase; PSD-93 – postsynaptic density protein 93; SDAT – senile dementia of the Alzheimer's type; SST – somatostatin; SSTRs1-5 – somatostatin receptors 1-5; STMS – seven-transmembrane segment receptor superfamily

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Table1. Location of SSTRs genes in human and mouse [92-93].

Receptor subtype	Human	Mouse
SSTR1	Chromosome 14 (14q21.1)	Chromosome 12 (12C1;12 25.61 cM)
SSTR2	Chromosome 17 (17q25.1)	Chromosome 11 (11E2;11 79.05 cM)
SSTR3	Chromosome 22 (22q13.1)	Chromosome 15 (15E1;15 37.55 cM)
SSTR4	Chromosome 20 (20p11.21)	Chromosome 2 (2G3;2 73.44 cM)
SSTR5	Chromosome 16 (16p13.3)	Chromosome 17 (17A3.3;17 12.62 cM)

STRUCTURE OF SOMATOSTATIN RECEPTORS

All somatostatin receptor subtypes are characterized by similar structural elements, however each of them has a specific primary structure. A common feature of mammalian SSTR1-5 is the presence of seven transmembrane α-helical segments, typical of hepta-helical receptors belonging to GPCR [14]. All SSTRs subtypes have relatively high amino acid sequences homology (in the range of 37 to 59%) [14,18,19] and are characterized by a homologous sequence of the structural motif in the seventh transmembrane domain [14]. Somatostatin receptors are located on different chromosomes depending on the species and subtype of the receptor. Examples of gene localization in human and mouse are presented in table 1. The expression of genes encoding somatostatin receptors is relatively complicated, as described in the paper published in 2003 by Moller et al. [20].

Human SSTR1 and SSTR2 are monomers composed of 391 and 369 amino acids respectively. They are characterized by the structure typical for the family of receptors containing seven transmembrane segments, where the conformation is constrained by the alternating arrangement of hydrophobic and hydrophilic protein segments [21]. The human SSTR3 receptor is composed of 418 amino acids, and its primary structure is similar to SSTR1 in 62%, to SSTR2 in 64% and to SSTR4 in 58%. SSTRs do not contain introns in the protein coding region [22]. Human SSTR4 consists of 388 amino acids and represents homology to SSTR1 (75%), SSTR2 (66%) and SSTR3 (67%) [23]. In the case of SSTR5, it was shown that the gene encodes a protein containing 383 amino acids and is homologous in 56-67% to other representatives of this subpopulation [24]. SSTRs are characterized by a high level of similarity in molecular structure between species [25]. In the case of SSTR2, two subtypes resulting from alternative splicing was distinguish: SSTR2a consisting of 369 amino acids and SSTR2b containing 346 amino acids in primary structure in mice [26-27]. On the other hand, for SSTR5, several variants of the shorter version of receptor were found, resulting from atypical splicing. These shorter versions have one transmembrane domain in the rat; one, two or four domains in mice and up to four or five in the human [28].

There are a number of substances, both endogenous and exogenous, which have an affinity for somatostatin receptors, acting as their agonists and antagonists. Some of them are specific to a particular type of receptor, while other are not. The most frequently used nonspecific agonist is the cyclic hexapeptide - pasireotide (the list of the most commonly used agonists for each receptor is shown in table 2). Radiolabeled agonists and antagonist of somatostatin receptor are used to visualize and target tumors in cancer therapy with radioactive isotopes [29].

All SSTRs in mammals show an equivalent binding strength of both active forms of somatostatin with the exception of SSTR5, which binds more strongly to SS28 than SS14 [30]. Individual receptor subtypes are characterized by specific similarities and differences in the mechanism of intracellular signal transmission as summarized in table 3. Based on structural and functional features as well as pharmacological properties, somatostatin receptors can be divided into two groups: first group, containing SSTR2, SSTR3 and SSTR5 and second one, including SSTR1 and SSTR4. The first group of the receptors is characterized by the signal transduction *via* Gi/G0 and Gq/G11 proteins while the second group only *via* Gq/G11 proteins [30].

Noteworthy feature of SSTRs is their ability to create homo- and heterodimers. Each receptor is able to couple with the same subtype, forming homodimers. In addition, heterodimers may be formed through functional and structural association of various somatostatin receptor subtypes (Tab. 4). Some SSTRs may form functional dimers also with other receptors belonging to the GPCR, as described later in this paper. Dimerization of SSTRs subtypes, especially the formation of heterodimers, generates new receptors with unique pharmacological and biochemical properties, which are different from the native receptor presented as monomers or homodimers [31]. An example illustrating the dimerization of SSTRs with another receptor belonging to the GPCR is the combination of SSTR5 and the cannabinoid receptor type 1 (CB1R). Zou et al. [32] investigated the co-localization of these receptors in rat brain as well as their internalization, interactions and signal transduction pathways on the HEK-293 cell line infected with human CB1R

Table 2. Selective agonists of somatostatin receptors [94].

	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
Selective agonists	L-797,591, Des-Ala 1,2,5-[D-Trp8, IAmp9]SRIF	L-054,522, BIM 23027, octreotide	L-796,778	L-803,087	BIM 23052, L-817,818

Table 3. Properties and distribution of somatostatin receptor in the brain [30].

	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
Synaptic localization	Mostly presynaptic	Postsynaptic	Extrasynaptic (Neuronal cilia)	Postsynaptic	Postsynaptic
Distribution in the brain	**High level**: amygdala, cortex, hippocampus, hypothalamus	**High level**: amygdala, cortex, hippocampus, hypothalamus	**High level**: amygdala, cerebellum, cortex, hippocampus, olfactory bulb, striatum		**High level**: hypothalamus, preopticarea
	Medium level: cerebellum, midbrain, spinal cord, striatum thalamus	**Medium level**: cerebellum, midbrain, striatum, spinal cord, thalamus	**Medium level**: hypothalamus, midbrain, preoptic area, thalamus	**Medium level**: amygdala, cortex, cerebellum, Hippocampus, olfactory bulb, preoptic area	**Medium level**: amygdala, cerebellum, cortex, hippocampus, striatum
Transduction	Gi/Go family	Gi/Go family, Gq/G11 family, G protein independent mechanism	Gi/Go family, Gq/G11 family	Gi/Go family	Gi/Go family, Gq/G11 family
Effectors	adenylate cyclase; protein tyrosine phosphatase; phospholipase C; Na^+/H^+ exchanger AMPA/kainate CA^{2+} channels K^+ channels	adenylate cyclase; protein tyrosine phosphatase; phospholipase C; phospholipase D; MAPK AMPA/ kainate CA^{2+} channels K^+ channels	adenylate cyclase; protein tyrosine phosphatase; phospholipase C; phospholipase D; MAPK AMPA/kainate CA^{2+}channels K^+ channels	adenylate cyclase; protein tyrosine phosphatase; phospholipase C MAPK; Na^+/H^+ exchanger; phospholipase A; CA^{2+} channels K^+ channels	adenylate cyclase; protein tyrosine phosphatase; phospholipase C MAPK; CA^{2+}channels K^+ channels

and SSTR5. They demonstrated the co-localization of the receptors in rat hippocampus, striatum and cerebral cortex, whereas studies on the cell line provided information on the presence of heterodimers of both receptors which were dissociated during treatment with an agonist. It was also shown that heterodimer activation causes formation of SSTR5 homodimer with parallel dissociation of CB1R. The cAMP-mediated transmission was modified in these studies mainly through the agonist of SSTR5 and this effect depended on its concentration [32]. Researchers highlight that the results of these studies may contribute to a better understanding of the biological effects of these receptors' interaction with ligands, which may be related to processes such as cell proliferation, neuroprotection or pain. Moreover, an insight into the structure, functions and signaling pathways of SSTR subtypes in the future may be the base of drugs designing in the treatment of neurodegenerative diseases and cancers of various origins.

Table 4. Formation of heterodimers by somatostatin receptors [95-96].

Receptor	Heterodimerisation
SSTR1	SSTR4; SSTR5
SSTR2	SSTR3; SSTR5
SSTR3	SSTR2
SSTR4	SSTR1; SSTR5
SSTR5	SSTR1; SSTR2; SSTR4

RECEPTOR-MEDIATED BIOLOGICAL ACTIVITY OF SOMATOSTATIN

The interaction of SSTRs with agonists induces a series of biochemical reactions in effector cells. Activation of somatostatin receptors in the brain causes an inhibition of adenylyl cyclase, decrease of intracellular Ca^{2+} level, K^+ channels-mediated cell hyperpolarization [20,30,33], protein phosphatases activation and mitogen-activated protein kinases (MAPKs) modulation [34]. Selected effectors specific for each subtype of SSTRs signaling pathways are shown in table 3.

Intercellular communication *via* SST is important for the functioning of the central nervous system and affects

cognitive functions such as learning and memory [35]. Somatostatin modulates neuronal activity by changing the response of AMPA/kainate receptors to glutamate (activation of SSTR1 and SSTR4 strengthens this response, whereas SSTR2 weakens) [20,30]. In this way somatostatin can influence such processes as rapid synaptic transmission and long term potentiation, which was confirmed for the SSTR3 [36]. In rodents, increased concentration of somatostatin in the brain has been shown to result in more effective learning of behavioral tasks, while a decrease in SST level by cystamine application (inhibitor of SST synthesis) resulted in impaired associative fear memory [37]. The results of these studies, together with disturbances in somatostatin transmission observed in patients with Alzheimer's disease (AD), which are described later in this paper, strongly suggest the fundamental role of SST in cognitive functions modulation.

The somatostatin system is also involved in the regulation of reproductive functions. It has been shown that SSTR1 is the one of the most important receptors involved in the signaling pathway necessary for the kisspeptin release (a peptide involved in the release of steroid sex hormones by gonadotropin-releasing hormone (GnRH) secreting neurons) [38]. Somatostatin neurons are associated with central regulation of reproduction [39] and are present in the same areas of the hypothalamus as the kisspeptin. Recent studies also suggest that somatostatin is involved in GnRH and luteinizing hormone secretion in sheep and this effect can be modulated by interaction with SSTRs [40]. In rat studies, all subtypes of SSTRs were expressed on the surface of GnRH neurons [41].

Moreover, somatostatin was shown to cause perimenopausal changes that affect hippocampal functioning [42]. During menopause, the supply of steroid sex hormones produced by the ovaries (such as estrogen and progesterone) to the hippocampus gradually weakens, causing impairment of learning ability, memory processes and spatial navigation [43-44]. Studies have shown that after ovariectomy-induced menopause in the female rats' hippocampus, the expression of vasoactive intestinal peptide, SSTR1, as well as other neuropeptides and their receptors was decreased. This may be directly related to the hippocampal plasticity dysfunctions observed during menopause, which indicates the involvement of SSTR1 in these processes [42].

SSTR2 plays an important role in regulating the food and water uptake, as shown in rodents. Activation of this receptor in the brain stimulates orexin signaling pathways and at the same time inhibits the secretion of leptin in the hypothalamus, resulting in increased appetite. Stimulation of SSTR2 also increases thirst by renin-angiotensin-aldosterone modulation [45]. Thus, SSTR2 activation is an important part of the mechanisms underlying the stimulation of food intake and increased water intake.

Another substantial function of somatostatin receptors in the brain is associated with mood regulation and involves the interaction of two systems - dopaminergic and somatostatinergic. It has been shown that SSTR2 is involved in emotional processes and disorders such as an anxiety, stress and depression [46]. Interestingly, mice expressing SSTR2 has a high level of corticosterone (a chronic stress marker) and exhibits anxiety behavior, whereas depression behaviors have been observed in mice with silenced expression of both SSTR2 and SSTR4 [47]. In the same study it was also shown that the administration of SSTR2 and SSTR4 agonists (but not SSTR1 and SSTR3) to the hippocampus causes a rapid blocking of the stress-activated hypothalamic-pituitary-adrenal axis and increases anti-anxiety and anti-depressant effects in behavioral tests. Studies conducted by another team show, that silencing the expression of SSTR4 results in increased susceptibility to stress in mice [48]. Moreover, it has been shown that chronic antidepressant intake affects the release of both dopamine and somatostatin in the nucleus accumbens [49-50]. The basis of the molecular mechanism responsible for this phenomenon are the interactions between the dopamine receptor type 2 (D2R) and SSTR5. The interaction of these receptors in the striatal interneurons and they ligand-dependent heterodimerization has been demonstrated. A study by Szafran-Plich *et al*. confirmed that exposure to antidepressants increases the number of D2R/SSTR5 heterodimers, which seems to prove the hypothesis that these heterodimers may be mediators of antidepressant effects [51]. Studies conducted by the same team have shown that also SSTR2 is involved in the response to antidepressant treatment and like SSTR5, it is associated with D2R and dopamine levels [52]. Another team of researchers showed that electroconvulsive therapy, successfully used in the treatment of depression, causes changes in the synthesis of SSTRs and ligands binding within the mice cortex and hippocampus [53]. The data collected so far seems to confirm the participation of SSTRs in the mechanisms of mood and fear regulation.

SSTRs show similar interactions with cannabinoid and opioid receptors as with dopaminergic receptors. As previously mentioned, SSTR5 forms heterodimers with CB1R, which is a member of the GPCR family. CB1R is highly expressed in the central nervous system and plays a key role in neurotransmission, neuromodulation and synaptic plasticity after activation by endogenous ligands - endocannabinoids [54]. Despite the many positive effects of cannabinoids in the nervous system (neuroprotective, anti-depressant and anti-epileptic), their application in medicine is limited by strong side effects. Heterodimerization of the SSTR5 and CB1R results in the formation of a receptor with new pharmacokinetic properties. Better understanding of this process may contribute to the development of a therapy that eliminates the side effects of cannabinoids.

Similar assumptions are being made for the SSTR4 interaction with the opioid delta receptor (δOR). The involvement of somatostatin receptors in the pathways of pain transmission has been demonstrated by silencing the expression of the SSTR4 in mice, which caused them to be more susceptible to pain than the wild type animals [55]. Opioids are the most effective therapeutics in pain relief, but their chronic use causes addiction. The possibility of analgesic properties by SSTR4 / δOR heterodimers raises hope for the development of a therapy that minimizes the risk of addiction and withdrawal effects [56].

Somatostatin belongs to neuropeptides involved in the mediation of not only pain but also itch. Neurons expressing dynorphine, crucial for itch perception, are stimulated through SSTR2a activation. The signaling pathway of itch involving SST is activated by the substances such as: gastrin-releasing peptide, natriuretic polypeptide B and histamine [57]. Further research into the role of SSTRs in pain and itch can provide tools for designing new, more effective and with less side effects therapeutic strategies.

SSTRs EXPRESSION IN THE BRAIN

Somatostatin is used as a marker for identification of the second most numerous subpopulation of GABA-ergic cortical inhibitory interneurons, modulating directly or by disinhibition the activity of excitatory cells [58]. Neurons expressing somatostatin play a significant role in learning and brain plasticity [30]. Somatostatin exerts biological effects by acting through SSTRs localized both pre- and postsynaptically, in several brain structures and circuits, and within different cell parts (e.g. soma, dendrites). Studies utilizing radioactive somatostatin have shown that SSTRs are widely expressed in the human brain, including regions crucial for cognitive and emotional functions, such as the cerebral cortex (mainly deep V-VI layers), limbic system or basal ganglia [59]. A similar pattern of SSTRs distribution was observed in the rat brain, with only a few differences [60]. More recent studies employing immunohistochemical techniques, allowed for more detailed assessment of the specific receptor types location in brain structures and synaptic localization, as shown in table 3. SSTR1 acts mainly as a presynaptic response modulator, while SSTR2 mainly participates in the postsynaptic responses. Interestingly, SSTR3 is expressed mainly in primary neuronal cilia. SSTR4, as SSTR2 is mainly located in the post-synaptic part [61]. Compared to other receptors in the brain SSTR5 expression is relatively low. However, it seems these receptors have functional significance, since a decrease in their expression was observed in neurological diseases [32].

The autoradiographic studies carried out at the beginning of the 90s of the last century on mature neocortex showed that somatostatin receptors are found mainly in layers V-VI, and less intense in layers I-IV [62]. Bolonga and Leorux study extended this knowledge, demonstrating the highest density of receptors in the cortical layer V, with a similar level of binding to SSTR1 and SSTR2. Studies employing *in situ* hybridization have shown an equivalent expression of mRNA for SSTR1 and SSTR2 in deep layers, while in layers I-III more mRNA for SSTR1 and less mRNA for SSTR2 was detected [63]. These data corresponds with the results of immunohistochemistry, confirming the location of the SSTR1 and SSTR2 proteins in the same cortical layers in which their mRNA occurs [64-66]. High level of SSTR2a protein was observed both in the cell body and in the dendrites of the pyramidal neurons of the layer V and lower level was detected in the layers I-IV of adult rats cortex [66].

Signaling *via* somatostatin receptors seems to play an important role in brain development, both in pre- and postnatal phase. SSTR1-5 are expressed in entire rat brain with the prevalence of the SSTR2 in the prenatal period [67]. In the first stage of neonatal period (P4-P7), strong expression of SSTR1 is visible, followed by SSTR3 and SSTR5 (P7-P14) and finally of SSTR4 (about P21). In the adult cortex, the SSTR1 and SSTR2 are dominant with an unique pattern of expression in single cortical layers [67].

Recent studies indicate the effect of somatostatin on the brain inhibitory system and GABA-ergic interneurons. The large morphological diversity of inhibitory interneurons allows for specific communication with postsynaptic neurons, controlling their excitability and modulate synaptic transmission. The key cortical interneurons are parvalbumin and somatostatin containing cells. First of them regulate the excitability of pyramidal neurons and the generation of the action potential propagating onto the cell body, the axon initial segment and proximal dendrites of pyramidal neurons, while somatostatin interneurons control signal integration and synaptic plasticity by affecting more distal dendrites [68].

Somatostatin may also affect the inhibition of neurotransmission through astrocytes. Astrocytes have a significant impact on both stimulatory and inhibitory transmission through gliotransmitters [69]. Within adult mice somatosensory cortex SSTR4 form heterodimers with GABA-B2 receptors localized on the peri-synaptic astrocyte protrusions. Both optogenetic activation of somatostatin interneurons and administration of somatostatin induces SSTRs-dependent activation of astrocytes, recorded by calcium imaging which suggests that astrocytes are functional component of the inhibitory network in the brain [70].

SSTRs IN THE PATHOLOGIES OF THE NERVOUS SYSTEM

Somatostatin receptors are involved in the pathogenesis, development and prognosis of glial tumors. High correlation was observed between the SSTRs expression and the stage of astrocytoma and glioma. Based on molecular and histological features that correlate with malignant tumor potential, astrocytic brain tumors are classified to WHO stage I-IV tumors [71]. Overexpression of the receptors for regulatory peptides was shown in many tumors, including these of astrocytic origin. This hallmark is useful during designing diagnostic methods and modifying of cancer therapy. Overexpression of SSTRs has been found in well-differentiated neuroendocrine gastrointestinal neoplasms (GEP-NEN) so far [72]. Over 80% of GEP-NEN in the first and second stages of development expresses somatostatin receptors, especially SSTR2a [72]. The results of studies of the SSTRs expression in glial tumors are inconclusive and the researchers are primarily focused on the expression of SSTR2 in high-grade tumors. Some of them show significant SSTRs expression in brain tumors [73-75] while others do not mention noticeable expression [76-77]. However, the latest studies conducted on a group of 57 astrocytic tumors patients [75] show some expression of SSTR2, SSTR3 and SSTR5 [75]. In studies employing immunohistochemistry, weak expression of somatostatin receptors in all tested samples of astrocytic origin tumors at stage I-IV has been demonstrated [75]. By analyzing the expression of specif-

ic SSTRs depending on the stage of neoplastic disease, the highest expression of SSTR2 at stage III, and SSTR3 at stage II and III was shown. In the case of SSTR5, relatively high expression of this receptor was demonstrated in the case of tumors in the II, III and IV stages. In the recent study, SSTR2, SSTR3 and SSTR5 expression was also found in peripheral microvasculature (SSTR2 in 37% of cases, SSTR3 44% and SSTR5 96%) [75].

Intercellular communication *via* somatostatin affects programmed cell death - apoptosis. It has been shown that in some cells SSTRs activation not only directly inhibits their proliferation, but also initiates apoptosis [76-77]. SSTR1, SSTR2 affect apoptosis of tumor cells and negatively affect the development of colon cancer cells, by reducing the expression of bcl-2 protein family [78]. However, in astrocytic tumors, somatostatin has no anti-proliferative effect (similar observation were made in neuroendocrine neoplasms as well) and in some cases may increase the proliferative effect of cancer cells [79].

It was shown that increased expression of SSTR1 contributes to neuronal apoptosis and is coupled with decreased expression of bcl-2 after intra-cerebral hemorrhage in rats [80]. Subsequent studies indicate a significant increase in SSTR3 expression around hematoma in rats with induced intracerebral bleeding, which correlated with increased neuronal apoptosis. It was also found that the increase in SSTR3 level is accompanied by an increase in the activity of p53, Bax and caspase-3 *in vivo* and *in vitro* [81]. All of these data suggests that somatostatin receptors may contribute in neuronal apoptosis after hemorrhagic stroke.

Somatostatin receptors are also involved in other nervous system pathologies, such as neurodegenerative diseases. Somatostatin is an essential inhibitory peptide involved in the aging process, both physiological and pathological [82-83]. In 1986, several neurotransmitter systems, including somatostatinergic were reported to be damaged in the senile dementia of the Alzheimer's type (SDAT). It was demonstrated that one third of patients with SDAT had decreased level of somatostatin receptors in the cerebral cortex [84]. In Alzheimer's disease, the level of somatostatin in the brain and cerebrospinal fluid decreases, which correlated well with cognitive functioning impairment and increased density of neurofibrillary tangles [85-87]. Another typical feature of AD is the impairment of olfactory system, which is related to the tau protein pathology within this brain structure [88]. In 2015 Martel *et al.* demonstrated that somatostatin neurons are abundant in mouse and human olfactory structures, which are strongly affected by tau-related pathological changes in AD. In aging mice reduced responses to olfactory stimuli were correlated with somatostatin system impairment in key regions of olfactory system [89]. Post-synaptic protein PSD-93 concentration was shown to ameliorate cognitive dysfunction in AD by enhancing β-amyloid catabolism, while concomitantly increasing expression of SSTR4. Researchers postulate that PSD-93 interacts with SSTR4 and affects the level of this receptor within the cell membrane. This mechanism is associated with ubiquitination of SSTR4, which occurs more intensively due to the inhibition of the enzymatic activity of PSD-93, and does not occur in the case of overexpression of this protein [90]. In the course of AD, not only the level of somatostatin in the cerebral cortex and in the cerebrospinal fluid decreases, but also the expression pattern of SSTR1-5 changes. The cerebral cortex of AD patients shows a significant reduction in the expression of SSTR4 and SSTR5 and moderate decrease in SSTR2 expression, without any SSTR1 level changes. The only receptor with increased expression in AD is SSTR3. Glial cells of AD patients show expression of SSTR1, -3 and -4, but not SSTR2 or 5. [91].

Somatostatin is a peptide that acts as a neurotransmitter and neuromodulator in the central nervous system. Recently, the knowledge about the involvement of SSTRs in physiology and various types of nervous system pathologies is rapidly developing. These receptors are involved in learning and memory processes, regulation of the inhibitory network in the brain, in pain and itch, mood changes, regulation of appetite and reproductive functions. SSTRs also play an important role in the development of neurodegenerative diseases, tumors and changes after hemorrhagic stroke. Increasing knowledge on the role of SSTRs in the pathology of the nervous system may contribute to the development of new therapeutic strategies in the future.

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Receptory somatostatynowe w mózgu

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Słowa kluczowe: somatostatyna, receptory somatostatynowe, układ nerwowy, mózg

STRESZCZENIE

Somatostatyna jest peptydem uczestniczącym w wielu szlakach biochemicznych i sygnałowych. Działa ona za pośrednictwem pięciu receptorów (SSTR 1-5) należących do rodziny receptorów sprzężonych z białkiem G. Wszystkie receptory somatostatynowe charakteryzują się znacznym stopniem homologii w budowie molekularnej i mogą oddziaływać ze sobą oraz niektórymi innymi receptorami tworząc strukturalne i funkcjonalne homo- lub heterodimery. Efekty komórkowe wywierane przez agonistów SSTR w tkankach obwodowych polegają głównie na hamowaniu uwalniania hormonów. W układzie nerwowym somatostatyna pełni również funkcje neuromodulatora i neurotransmitera wpływając na procesy pamięci, uczenia się oraz nastrój. SSTR są zaangażowane w regulację procesów fizjologicznych takich jak odczuwanie świądu i bólu, funkcje rozrodcze i pobieranie pokarmu. Poza funkcjami fizjologicznymi SSTR mają swój udział również w patogenezie i przebiegu nowotworów pochodzenia glejowego, chorób neurodegeneracyjnych czy zmian po udarze krwotocznym. Ostatnie lata dostarczają coraz więcej badań dotyczących roli szlaków sygnalizacyjnych receptorów somatostatynowych w mózgu, a wiedza na ten temat wciąż dynamicznie się rozwija.