OLD AND NEW NEUROENDOCRINE MOLECULES: SOMATOSTATIN, CYSTEAMINE, PANTETHINE AND KYNURENINE

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The aim of this review is to commemorate Hans Selye, endocrinologist, the most famous researchers of stress and to briefly summarize the major features of somatostatin (SST), cysteamine (CysA) and patethine (PAN) in neuroendocrinological aspect, which are closely related to his scientific work. In addition, some metabolites of kynurenine pathway (KP) were also mentioned in this paper, as new, possible target molecules in neuroendocrinology.
R. Guillemin and A. V. Schally were the main pioneers of the discovery of SST in the 1970's. SST primarily is known as an inhibitor of growth hormone secretion and additionally reduces the gastric acid and pepsin release and also the gastroduodenal mucosal blood flow. These effects are very important in the pathophysiology of peptic ulcer bleeding, which is related to the CysA-evoked perforating duodenal ulcer experimental stress model in rats developed by Selye and Szabo. CysA is a naturally occurring duodenal ulcerogen, which depletes SST in the gastric mucosa and certain brain regions. Furthermore, in addition to depleting SST, CysA also causes adrenocortical necrosis, suggesting an interaction between the central/peripheral nervous system and the neuroendocrine system. The antioxidant PAN, formulated besides the CysA, has similar effects: it attenuates the levels of SST and prolactin in the cerebral cortex and hypothalamus through the accumulation of CysA within cells throughout the body. As new perspectives the KP may be involved in the modulation of neuroendrocrine processes: different agonists and antagonists of glutamate receptors regulate the hypothalamic-pituitary-adrenal axis and kynurenic acid augments the anxiolytic stress responses in neonatal chicks. The pro-inflammatory cytokine-induced and the toxic heavy oil contaminations-evoked alterations in the KP indirectly contribute to the development of neuroendocrine disorders.
In summary, there have been highly important developments in neuroendocrinology since the early findings of Selye. Although there are as yet relatively few data about the potential role of kynurenines in neuroendocrinology, the results already achieved are extremely noteworthy and immensely promising.

Keywords: *somatostatin, cysteamine, pantethine, kynurenine*

RÉGI ÉS ÚJ NEUROENDOKRIN MOLEKULÁK: SZOMATOSZTATIN, CISZTEAMIN, PANTETHIN ÉS KINURENIN

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Ideggyogy Sz 2014;67(3–4):000–000.

Az összefoglaló célja, hogy megemlékezzünk Selye Jánosról, az endokrinológia, a stressz leghíresebb kutatójáról, és röviden összefoglaljuk a szomatosztatin (SST), a ciszteamin (CysA) és a pantethon (PAN) legfontosabb jellemzőit neuroendokrinológiai szempontból, amelyek szoros összefüggésben állnak tudományos munkájával. Emellett megemlítjük a kinurenin (KP) -útvonal néhány metabolitját is mint a neuroendokrinológia néhány lehetséges célmolekuláját.
R. Guillemin és A. V. Schally jártak elől az SST felfedezésében az 1970-es években. Az SST-t főként a növekedésihormon-elválasztás inhibitoraként ismerjük, emellett csökkenti a gyomosav és a pepszin felszabadulását és a gastroduodenalis nyálkahártya véráramlását. Ezek a hatások nagyon fontosak a peptikus fekély vérzésének kórélettanában, ami összefügg a CysA által kiváltott perforáló duodenalis fekély kísérletes stresszmodelljével, patkányban, amit Selye és Szabó fejlesztettek ki. A CysA a természetben előforduló duodenalis ulcerogen anyag, ami SST-depléciót okoz a gyomornyálkahártyában és egyes agyi régiókban. Az SST-depléció mellett a CysA adrenocorticalis necrosist is okoz, ami kölcsönhatásra utal a centrális/perifériás idegrendszer és a neuroendokrin rendszer között. A CysA mellett képződő antioxidáns PAN hatása hasonló: csökkenti az SST és a prolaktin szintjét az agykéregben és a hypothalamusban az által, hogy a CysA testszerte felhalmozódik a sejteken belül. Új szempontként a KP részt vehet a neuroendokrin folyamatok modulációjában: a glutamátreceptorok különböző agonistái és antagonistái szabályozzák a hypothalamus-hypophysis-mellékvese tengelyt, és a kinurénsav fokozza újszülött csibékben az anxiolyticus stresszválaszt. A KP proinflammatorikus citokin által indukált és a toxikus nehézolaj-szennyeződés által kiváltott változásai közvetetten hozzájárulnak a neuroendokrin zavarokhoz. Összességében nagyon fontos fejlődés ment végbe a neuroendokrinológiában Selye első eredményei óta. Bár még viszonylag kevés adatunk van a kinureninek potenciális szerepéről a neuroendokrinológiában, a már elért eredmények különösen értékesek és nagyon ígéretesek.

Kulcsszavak: *szomatosztatin, ciszteamin, pantethin, kinurenin*

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Érkezett: 2013. november 20. Elfogadva: 2014. február 10.

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The hormone *somatostatin (SST)* was isolated from the hypothalamus in the 1970's[1-3]. It was originally regarded only as an inhibitor of growth hormone (GH) release (and was previously called somatotropin release inhibiting factor), but it is now known that SST has a number of biological effects. *Burgus* et al. observed that the addition of crude extracts of the ovine hypothalamus to anterior pituitary cells maintained in vitro inhibited the secretion of GH and they isolated a compound that accounted for all the GH-release inhibiting activity of the crude extract[1]. After sequencing and synthesis the peptide displayed biological activity both in vitro and in vivo. SST, a small cyclic peptide, exists in two biologically active forms: SST-14 and SST-28, which are produced by the alternative post-translational cleavage of the single prehormone. SST release can be stimulated by a variety of hormones (growth hormone- and corticotropin-releasing hormone, neurotensin), neuropeptides, neurotransmitters, cytokines, growth factors and nutrients in several tissues[4]. On the other hand, the neurotransmitter GABA and opiates generally inhibit SST secretion[5]. Inflammatory cytokines, such as interleukin-1, tumor necrosis factor alpha and interleukin-6, are potent stimulators of SST release[6], while transforming growth factor beta and leptin[7] inhibit the secretion of the peptide. The development of synthetic analogs has led to the effective treatment of clinical disorders including acromegaly, hormone-secreting tumors of the gastrointestinal tract and portal hypertensive bleeding[4]. As a general inhibitor of gastrointestinal endocrine secretion, SST inhibits both gastric acid and pepsin release[8]. Moreover, it combines these effects with a reduction in gastroduodenal mucosal blood flow, which appears to be important in the pathophysiology of peptic ulcer bleeding. These results were demonstrated by several experimental stress models; one of the earliest of these was the cysteamine-evoked perforating duodenal ulcer model in rats developed in 1973 by *Selye* and *Szabo*[9].

Cysteamine (CysA) is a small aminothiol generated by hydrolysis of the lipid-lowering drug *pantethine (PAN)*, together with two pantothenic acids (vitamin B5). It is assumed that CysA is involved in the production of cholesterol and triglycerides by means of its binding to inactivate sulfur-containing amino acids in liver enzymes. Moreover, CysA is a naturally occurring duodenal ulcerogen and has the ability to cause adrenocortical necrosis too[10]. CysA and its derivatives deplete SST in the gastric mucosa, causing significant increases in gastric acidity and pepsin activity, alterations that contribute to the development of duodenal ulcer[9]. The ulcerogenic activity of these derivatives is significantly correlated with their SST-depleting activity[11]. In accordance with these findings, the administration of SST prevents the development of CysA-induced duodenal ulcer. However, the effects of CysA in causing duodenal ulcer and adrenal lesions suggest an interaction between the central/peripheral nervous system and the neuroendocrine system. In 1982, *Palkovits* et al. demonstrated that a single subcutaneous (sc.) injection of CysA (300 mg/kg) resulted in a quite selective SST depletion in the brain. An approximately 70–80% decrease in SST levels was observed in those areas where SST-producing neurons (periventricular nucleus) and SST-ergic nerve terminals (median eminence) are located, whereas the CysA did not produce changes in the levels of other neuropeptides[12].

The naturally occurring antioxidant PAN is a stable disulfide precursor of pantetheine. The latter is an intermediate in the production of coenzyme A (CoA) in the organism **(Figure 1.)**. From a biochemical aspect, the enzymatic cleavage of PAN produces CysA (and later taurine) and pantothenic acid. After absorption from the food, 4'-phosphopantetheine is reformed by the action of pantothenate kinase, after which ribose and adenine molecules attach to it in the mitochondrium to create CoA or bind to acyl carrier protein[13]. CoA and acyl carrier protein function as acyl or acetyl carriers. CoA facilitates the transfer of acetyl groups from pyruvate to oxaloacetate, thereby initiating the Szent-Györgyi–Krebs (tricarboxylic acid) cycle. CoA is involved in several ways in the fat metabolism, including the synthesis, transportation and degradation of fatty acids. Several clinical studies

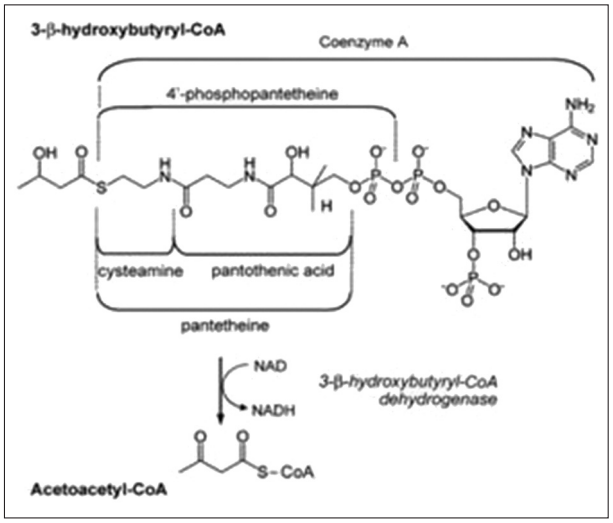

Figure 1. *Metabolic pathway of pantethine (ImageCLEF 2011-Medical Datasheet)*

have demonstrated its moderate benefits on dyslipidemic subjects[14] and also its inhibition of platelet aggregation, which offers an effective therapeutic option for the treatment of patients with different forms of atherosclerotic vascular disease[15].

From a neuroendocrinological aspect, the administration of PAN attenuates the levels of SST- and prolactin-immunoreactivity in the cerebral cortex and hypothalamus[16] through the accumulation of CysA within cells throughout the body. It has therefore been suggested that this substance may be a useful pharmacological tool for elucidation of the role of SST in the central nervous system. The function of catecholaminergic pathways cannot be excluded completely since PAN or possibly the forming CysA inhibits dopamine beta-hydroxylase[17]. In 1989, *Sellini* et al. observed that a single high dose of PAN increased the levels of adrenocorticotropic hormone and cortisol (still within the normal range), but had no effect on the GH and Pro levels. This might be explained by a PAN-induced stimulus of the pituitary–adrenal axis or an increased synthesis of acetylcholine[18].

There is evidence that CysA and PAN have behavior-modulating functions and other hormonal effects too. CysA can more effectively diminish locomotor, rearing and grooming activities than an equimolar dose of PAN. PAN influences several other behavioral responses in animals[19]: it stimulates the food intake in satiated rats, depending upon the stage of the circadian rhythm, but inhibits the food intake in fasted animals[17]. This effect is possibly mediated through the disinhibition of central appete-regulating SST-ergic pathways. It influences shuttle box learning[20] and causes locomotor inhibition (4 h after sc. treatment) and activation (24 h after repeated sc. injection) in open-field test[21, 22]. It leads to the attenuation of SST-induced barrel rotation[23]. From the aspect of passive avoidance behavior, there is no effect after sc. administration and merely a slight disruption after intracerebroventricular (icv.) treatment[21]. CysA, and to a lesser extent PAN, reduced the concentration of noradrenaline and increased those of dopamine and 3,4-dihydroxyphenylacetic acid in the hypothalamus. Pantothenic acid itself did not influence either the hypothalamic catecholamine concentrations or the behavior of rats[22].

Kynurenines, as ligands of glutamate (Glu) receptors may also be important modulators of the neuroendocrine system. In 1976, *Coyle* and *Schwarcz* revealed that kainic acid (KA) is associated with lesions of the striatal neurons, as in Huntington's disease (HD) and it depletes SST[24]. In 1989, *Beal* et al. demonstrated that the striatal excitotoxin lesions caused by the injection of quinolinic acid (QA), resulted in relative sparing of the SST and neuropeptide-Y (NPY) levels in rats[25]. Cortical injections of certain agonists acting at the Glu receptors depleted the Glu and GABA levels, while the SST- and NPY immunoreactivity were either unchanged or significantly increased. Other N-methyl-D-aspartate (NMDA) excitotoxins, such as KA and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) caused significant decreases in the concentration of SST[26]. Chronic QA-induced lesions resulted in similar alterations: elevated SST and NPY concentrations and reduced GABA, substance P-ir and choline acetyltransferase activity[27]. The pattern of selective neuronal damage caused in the cerebral cortex by NMDA receptor agonists was similar to that observed in HD. However, there are contradictions, because there were no changes in SST, NPY or SP-ir with aging in the cerebral cortex or hippocampus following QA-induced striatal lesions[28], but there are different behavioral effects of KA- or QA-induced striatal lesions[29].

Preclinical studies have indicated that the kynurenine pathway (KP) may be involved in the modulation of neuroendrocrine processes. Especially the function of kynurenic acid (KYNA) as a new, potential neuroendocrine molecule is emphasized. The main branch (approx. 95%) of the tryptophan (Trp) metabolism is the formation of kynurenines. Trp may be converted to L-kynurenine (KYN) by Trp- or indoleamine 2,3-dioxygenase (IDO) via a transition product. KYN serves as a key molecule between the neurotoxic and neuroprotective directions of the pathway. The neurotoxic QA is produced from KYN via additional toxic metabolites, which generate toxic free radicals, oxidative stress and lipid peroxidation, and hence excitotoxicity. In contrast, the characteristically neuroprotective KYNA is formed directly from KYN catalyzed by kynurenine aminotransferase (KAT) **(Figure 2.)**[30]. Most of the neuroprotective, antiexcitotoxic effects of KYNA are explained by the inhibition of excitatory amino acid receptors. It has been proposed to act primarily as an antagonist at ionotropic AMPA and KA receptors, and as a noncompetitive antagonist at the strychnine-insensitive glycine-binding site of the NMDA receptors. KYNA can be an antagonist of the alpha7-nicotinic acetylcholine receptors, and a ligand for the orphan G protein-coupled receptors and the recently revealed aryl hydrocarbon receptors[31]. There is extensive literature on the role of the KP in different neurological diseases. Its protective impacts are emphasized in HD[32], Parkinson's disease[33],

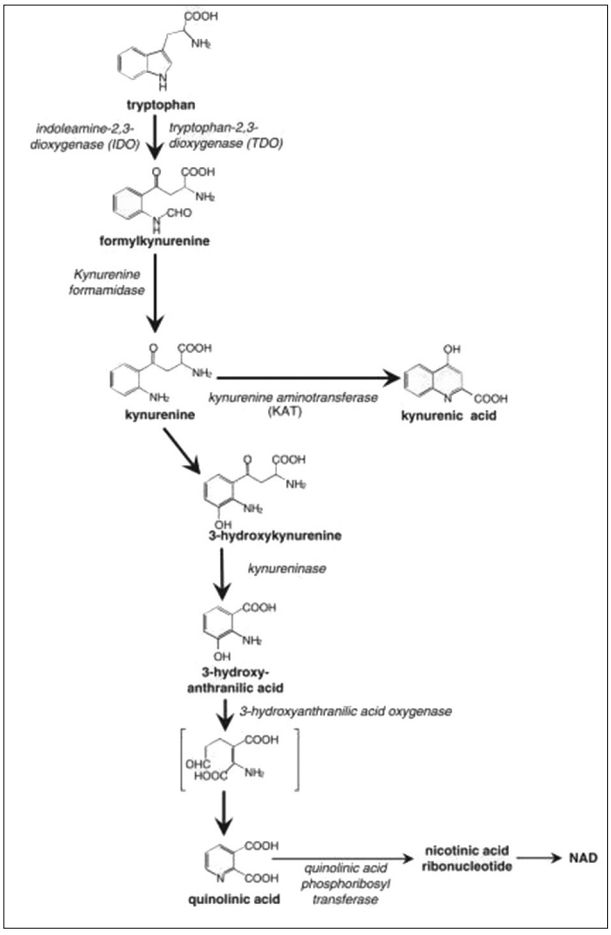

Figure 2. *Main pathway of tryptophan-kynurenine metabolism*

Figure 3. *Relationship between kynurenines, metabolic syndromes (MetS) and age-associated neuroendocrine disorders (AAND) (Oxenkrug, G.F. Ann N Y Acad Sci, 2010)*

migraine[34, 35], multiple sclerosis[36, 37], schizophrenia[38], stroke[39, 40] and epilepsy[41], but its action in endocrine/neuroendocrine mechanisms has not yet been fully investigated.

In 1985, Rogers and Evangelista observed that leucine-stimulated insulin release from rat pancreatic islets can be inhibited by kynurenine metabolites (3-hydroxykynurenine and 3-hydroxyanthranilic acid)[42]. The regulatory effects of QA were investigated in ovariectomized, estradiol-primed rats. It was shown that icv. administered QA evoked an acute, dose-dependent increase of serum luteinizing hormone concentrations, which was blocked by KYNA. Brain morphologic disturbances were not detected in consequence of the treatments[43]. The agonists and antagonists of Glu receptors regulate the hypothalamic-pituitary-adrenal axis (HPA) by different subtypes of amino acid receptors. Glu, KA and L-aspartate (Asp) significantly diminished the release of corticotropin-releasing hormone, while Asp and NMDA significantly enhanced arginine-vasopressin release, whereas this was decreased by KA and quisqualic acid. KYNA completely abolished the effects of Asp in connection with both neurohumoral activators[44]. A human study has indicated that cytokines such as interferon- and interleukin-10 regulate the expression of IDO in cells of hypothalamic and pituitary origin in connection with sickness behavior of patients[45]. In 2010, Oxenkrug observed similar results: the pro-inflammatory cytokines facilitate the activity of IDO, which shifts the Trp metabolism to the formation of kynurenines. These molecules indirectly contribute to the development of metabolic syndromes and age-associated neuroendocrine disorders via apoptotic, neurotoxic and pro-oxidative effects **(Figure 3.)**. A genetic predisposition to the presence of certain polymorphisms of pro-inflammatory cytokine genes might lead to the "superinduction" of IDO[46]. The anxiolytic effects of KYNA were recently evaluated in neonatal chicks. A stress model was developed by social isolation, which was augmented by icv. corticotropin-releasing hormone. The stress responses were decreased by the icv. administration of Trp and (more effectively) KYNA. Attenuated distress vocalization, active wakefulness and increased time of sleeping position were observed after the KYNA treatment. Moreover, a depressed plasma corticosterone concentration was measured[47]. When the toxic reverberations of the heavy oil spill near the northwest coast of Spain (2002) were examined seven years after the disaster from the aspects of endocrine and immunological alterations, the biomarker analyses revealed a significantly increased plasma level of cortisol, and decreased level of KYN and CD16+56+lymphocytes in exposed vs. unexposed individuals. More serious changes were observed in the chronically contaminated subjects, which suggested a chronic elevation of HPA activity and the possibility of endocrine diseases[48].

In summary, it may be stated that there have been highly important developments in neuroen-

docrinology since the early findings of Selye. Although there are as yet relatively few data about the potential role of kynurenines in neuroendocrinology, the results already achieved are extremely noteworthy and immensely promising.

ACKNOWLEDGEMENT

This work was supported by the following grants: TÁMOP-4.2.2. A-11/1/KONV-2012-0052, Neuroscience Research Group of the Hungarian Academy of Sciences and University of Szeged.

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