
Pain and epilepsy are not only pathophysiological process; there are also psychic phenomenons with a broad spectrum of individual variances, leading to serious medical and social problems. Therefore, investigations aimed at development of new effective analgesics and antiseizure are of great importance. The purpose of the present study was to investigate the effects of some MIF-1 analogues containing amino acids such as L-canavanine (L-Cav), L-Lysine (Lys) and L-Norleucine (Nle) on the nociception in rats and pentylentetrazol (PTZ) seizures on the mice. Being theoretically important, the results might also be of interest for the clinical practice, offering grounds for a new therapeutic approach for the treatment of pain and seizures.


Melanocyte-inhibiting factor (MIF-1) is a member of the Tyr-MIF-1 family. MIF-1 represents a class of naturally occurring opiate antagonists with varying activities in
independent situations. The purpose of the present study was to investigate the influences of MIF-1 on the antinociceptive effects of L-Arg, L-Orn and L-Cit (L-citrulline). The experiments were carried out on male Wistar rats. The changes in the mechanical nociceptive threshold were measured by the Randall-Selitto paw pressure test using an analgesimeter. MIF-1 (1 mg/kg) was administered intraperitoneally (i.p.), L-Arg, L-Orn and L-Cit were administered intracerebroventricularly (i.c.v.) at a dose 20 µg/20µl. MIF-1 decreased the antinociceptive effect of L-Arg and reversed antinociceptive effects of L-Orn and L-Cit into hyperalgesia.


Out previous data demonstrated that L-ornithine (L-Orn), L-canavanine (L-Cav), L-arginine (L-Arg) but not L-citrulline (L-Cit) exerted naloxone-reversible antinociceptive effects whereas L-canaline (L-Can) induced hyperalgesia in rats. We investigated the anticonvulsive effects of the amino acids (20 µg/mice, i.c.v.) on pentylenetetrazole (PTZ) (85 mg/kg, s.c.) seizure model in male mice. L-Cav in PTZ seizure model exerted strong inhibition of the seizure intensity compared with control group, but L-Orn, L-Arg and L-Cit had no influence. L-Can potentiated significantly the PTZ seizures. Most probably neurotransmitter mechanisms are involved in the realization of the observed anticonvulsant effect of L-Cav. The obtained data suggest that L-Cav can modulate seizure reactivity.


Pain, oedema and fever are the signs and symptoms of inflammation. Prostaglandins (PGs) are well established as mediators of several components of the inflammatory response. Particularly, PGs potentiating the microvascular effects of other mediators such as bradykinin, substance P and histamine. These mediators also induce pain in inflammatory sites and this component is also potentiated by PGs. Although PGs are not direct algesic agents as are bradykinin, substance P and histamine, they nevertheless induce a state of hyperalgesia in which previously non-painful stimuli are now perceived as painful in both animal models and in human subjects. It's known that nonsteroidal anti-inflammatory drugs (NSAID) inhibited the synthesis of prostaglandins and its derivatives.

We studied nine newly synthesized pyrrole derivatives based on the architecture of tricyclic
COX-2 inhibitors and bonded to salicylic (D37, D84, D87), isonicotinamide (D51, D52, D53) or pyrazolone (D54, D71, D73) moiety for analgesic activity. The effects on nociception were examined in male Wistar rats by the Randall-Selitto paw-pressure test. The compounds were administrated intraperitoneally (i.p.) in doses 10, 20 and 40 mg/kg. The results showed that pyrrole derivatives based on the architecture of tricyclic COX-2 inhibitors increased significantly the pain threshold. This effect is dose related and more pronounced in inflamed paw.


The Tyr-MIF-1 family of peptides includes MIF-1, Tyr-MIF-1, are endogenous neuropeptides with opiate modulating and other effects in the central nervous system. Tyr-MIF-1 is a novel peptide structurally related but immunoreactively different from MIF-1. Addressing this problem, we applied NADPH-d histochemistry and tyrosine hydroxylase and in order to determine distribution patterns of tyrosine hydroxylase (TH)-immunoreactive axonal elements and density of NADPH-d-reactive neurons in rat striatum treated with MIF-1 and Tyr-MIF-1 for similar properties. We used Wistar rats treated intraperitoneally with MIF-1 and Tyr-MIF-1 (1 mg/kg) to study the histochemistry for NADPH-d and the immunocytochemistry for TH in the striatum. Morphometric analysis was performed using a microanalysis system (Olympus CUE-2). Data were compared by Student’s t-test. In summary both investigated peptides may affect distribution patterns of TH-immunoreactive axonal elements and density of NADPH-d-reactive neurons in rat striatum.


The purpose of the present study was to investigate the influences of L-canavanine (L-Cav) and D-Arginine (D-Arg) on the antinociceptive effects of L-arginine (L-Arg), L-ornithine (L-Orn), L-citrulline (L-Cit), L-canaline (L-Can) and involvement of endogenous NO. The changes in the nociceptive effects were examined on rats in acute pain by paw pressure (PP), hot plate (HP) and tail flick (TF) tests. Our results showed that L-Cav and D-Arg significantly decreased the antinociceptive effects of L-Arg, L-Orn, L-Cit and L-Can. L-NAME significantly increased the antinociceptive activity of investigated amino acids, but
in combination L-NAME+SIN-1 decreased it. Our data suggest that in nociceptive activity of amino acids is involved endogenous nitric oxide (NO). L-Cav and D-Arg decreased the nociceptive effects of amino acids in different way.


Tyr-MIF-1 is a member of family of neuropeptides and showed anti-opioid and opioid-like actions. The N-terminal Tyr¹ ring is typical for endogenous opioid peptides and it is considered to be responsible for the opioid action. The aim of this study was to investigate the effects of four newly synthesized analogues of Tyr-MIF-1 with modified Tyr¹ residue: N-(Me)-Tyr-MIF-1, D-Tyr-MIF-1-(Me), Tyr(Cl₂)-MIF-1, Tyr(Br₂)-MIF-1. They were examined in male Wistar rats by two nociceptive tests - paw-pressure (PP) and hot-plate (HP). Non-competitive opioid-receptor antagonist naltrexone (Nal) was used to clarify whether opioidergic system was involved. The results showed that all investigated newly synthesized analogues applied alone exerted short lasting antinociceptive effects compared the control group but not versus Tyr-MIF-1 in both tests used. Naloxone decreased significantly their antinociceptive effects in PP and HP tests, we suggest an involvement of the opioidergic system in antinociceptive effects of N-(Me)-Tyr-MIF-1, D-Tyr-MIF-1-(Me), Tyr(Cl₂)-MIF-1 and Tyr(Br₂)-MIF-1.


Tyr-W-MIF-1 has been isolated from human cerebral cortex and bovine hypothalamus and is named for its structural similarity to the melanoocyte-stimulating hormone release-inhibiting factor-1 (MIF-1) family of brain peptides. Literature data show that Tyr-W-MIF-1 induced antinociception is prolonged and naloxone-reversible. Stressors are a potent modulator of opioid activities. Stress models such as immobilization, hot and cold exposure lead to release of endogenous opioid peptides which produce analgesia. This phenomenon is referred to as stress-induced analgesia (SIA). The purpose of the present study was to examine the involvement of naloxone (Nal) and methylene blue (MB) in the nociceptive effects of Tyr-W-MIF-1 after one hour of immobilization, cold or hot stress. Our results suggest that naloxone and methylene blue are differently
involved in the nociceptive effects of the endogenous neuropeptide Tyr-W-MIF-1 after immobilization, cold and hot stress. More pronounced effects were observed after one hour of immobilization and less pronounced were detected after one hour of hot exposure.


The purpose of the present study was to investigate the effects of Tyr-W-MIF-1 on nociception after one hour of immobilization, cold or hot stress (IS, CS and HS) and the involvement of nitric oxide. We suggest that the endogenous neuropeptide Tyr-W-MIF-1: (i.) has different effects on pain threshold after the three stress models used; (ii.) influences the NO-ergic system during the above mentioned kinds of stress through different mechanisms.


Leu-enkephalin analogue [Cys(O2NH2)2] enkephalin has been shown selective δ-opioid effect and stability to peptidases in “in vitro” experiments. The aim of this study was to determine the modulating effect of [Cys(O2NH2)2] enkephalin on stress-induced antinociception. Analgesia was tested using hot-plate (HP) and paw pressure (PP) tests after one-hour immobilization (IS) and hot (HS) stress. The test and referent substances were applied i.p. immediately after the stress. PP testing after IS and HS showed significantly greater nociceptive effect as compare to the control. [Cys(O2NH2)2]-enk and Leu-enk decreased the paw-withdrawal threshold. HP latency was significantly longer after both stress models and [Cys(O2NH2)2]-enk reduced the latency in the same manner as Leu-enk. The development of stress-induced analgetic response was prevented by Nal.

Various stress models have been reported to induce analgesia due to stress. This is a phenomenon, referred to as stress-induced analgesia. Exposure of an animal to stressful stimuli, perceived by the animal as a threatening, emergency condition, except nociception, induces a transient increase in core temperature. This response is often called stress-induced hyperthermia. There is literature data that decrease of pain sensitivity often affects thermoregulatory mechanisms in the threatened organism. The purpose of the present study was to compare changes in pain thresholds and core temperature after three models of acute stress: immobilization (IS), cold (CS) and hot (HS). Antinociceptive effects of the male Wistar rats were evaluated using the paw pressure and the hot plate tests. Temperature was measured with thermistor probes inserted rectally to a depth of 6 cm and monitored on multichannel recorder. The obtained results show that after IS, CS and HS there are significant increase in pain thresholds. The most pronounced was the effect in nociception after HS, but this effect was very short. Effects of IS and CS was not so powerful, but they were observed during the whole investigated 30th min period. After three models of stress increase in core temperature was observed during 15th, 30th and 45th min of the experiment. Only in the beginning of the experiment CS elicits hypothermic effect, while IS and HS significantly increased core temperature, most pronounced for HS. In conclusion IS, CS and HS induced nociceptive and temperature changes in rats, which are with different intensity and continuance.


Peptides of the Tyr-MIF-1 family – MIF-1 and Tyr-MIF-1 have antioioid and opioid-like effects. It’s known that stress leads to formation of excessive free radicals – extremely reactive and unstable chemical species, which are a major internal threat to cellular homeostasis of aerobic organisms. Furthermore opioid peptides have been recognized as modulators of reactive oxygen species (ROS). So far no data about direct scavenger properties of Tyr-MIFs peptides were available. The aim of our study was to investigate the antioxidant activity of MIF-1 and Tyr-MIF-1 after immobilization (IS), cold (CS) and hot (HS) stress in brain and blood plasma. We found that: i.) MIF-1 and Tyr-MIF-1 in intact animals showed antioxidant effects in brain and pro-oxidant – in blood plasma; ii.) MIF-1 and Tyr-MIF-1 after three different models of stress showed antioxidant effects on ROS in brain and blood plasma with exception of MIF-1 after HS in blood plasma; iii.) MIF-1 and Tyr-MIF-1 after IS and HS showed antioxidant activity on tissue damage in brain.

Stress is known to exert an influence on neuroendocrine, autonomic, hormonal, and immune functioning. Various stress models have been reported to induce analgesia. This is a phenomenon, referred to as stress-induced analgesia (SIA). One of the mechanisms known to play a part in the response of an organism to stress is activation of the endogenous opioid system. Endogenous opioid peptides take part in various functions as hormones or neuromodulators. Tyr-W-MIF-1 and Tyr-K-MIF-1 are neuropeptides, neuromodulators, which are able to inhibit the expression of some forms of SIA. Nitric oxide (NO) plays an important role in initiation and maintenance of pain. It is also known that acute and chronic stress induce biochemical changes affecting both pain threshold and behavior. Thus, endogenous opioid peptides and nitric oxide (NO), mediated a wide variety of physiological processes including pain transmission and SIA. The aim of the study was to investigate the effects of Tyr-W-MIF-1 and Tyr-K-MIF-1 on nociception after immobilization, hot and cold stress (IS, CS and HS) and NO-involvement. L-Arginine, L-NAME and SIN-1 were used. Nociception was measured in male Wistar rats by paw pressure (PP) test. In conclusion we suggest that there is a different kind of involvement of endogenous nitric oxide in the mechanisms of nociception of Tyr-W-MIF-1 and Tyr-K-MIF-1 after immobilization, cold and hot stress.


Nitric oxide (NO) synthesized by the enzyme nitric oxide synthase (NOS) affects the secretion of stress hormones and NO system is a stress-limiting system. Also, NO is involved in NO-molecular ways, which affect through auto regulation different signaling molecules - like opioids, endocannabinoids and others. Many stress models have been reported to affect the levels of nitric oxide and stimulate the expression of NOS engaged in their synthesis. Stimulation of opioid receptors within the periaqueductal gray (PAG) activates descending opioid and noradrenaline inhibitory pathways and suppresses nociception. Because PAG has been identified as region that mediates the response to different stressful paradigms and contains distinct, longitudinally organised neural substrates, our goal was to investigate the effect of 3 hours immobilization stress (IS) on
NO activity in rat ventrolateral PAG (vIPAG) by a histochemical procedure for nicotinamide adenine dinucleotide phosphate-diaphorase (NADPH-d). According to obtained data NADPH-d reactive neurons in rat’s vIPAG and NO activity respectively was increased by stress model mentioned above.


The basal nuclei (BN) have been involved in stress response and nociceptive perception. They are complicated complex of internal anatomical and neurochemical organization that receive input from many brain areas includes the cortex and sends output to other components of the brain. They are designed to protect the individual through basic “drives” such as self preservation, bodily appetite and fear. The endocannabinoid system is a recently identified neuromodulatory system involved in several physiological and pathophysiological processes. Endogenous cannabinoids are important signaling molecules in neuroendocrine control of homeostatic and reproductive functions including stress response and energy metabolism. The aim of the present study was to examine the expression of endocannabinoid CB1 receptors after acute cold stress. We suggest that increased by cold stress CB1-immunoreactivity in rat’s BN is possible protective role of CB1 receptors in stressful condition.


The prefrontal cortex (PFC), which mediates the emotional coping response to different stressful paradigms, is composed of distinct parts depends on stimulus involved physical or psychological stress. It also plays a role in a number of neurological conditions. It’s known that neuroendocrine control of homeostatic and reproductive functions including stress response and energy metabolism is fulfilled by important signaling molecules as endogenous cannabinoids. The aim of the present study was to examine the effects of cold stress on distribution of CB1 receptors in PFC of rats. Immunohistochemical procedure for CB1-receptors was performed in adult male Wistar rats. The data were entered in the computer program, recorded automatically, calculated and compared by Student’s t-test. We found
CB1-immunoreaction in axons and dendrites as well as in cell bodies where they presented as puncta on somata. The cells bodies were comprised of several distinct shapes: pyramidal, oval, fusiform and multipolar. Numerous fine-beaded fibers and puncta were seen on a handful of pyramidal large-sized neurons and many puncta were observed around the oval-shaped small- and medium-sized neurons. The PFC in cold stress rats demonstrated around 18% higher density of CB1-receptors compared with controls. In conclusion our results showed that cold stress exposure increased distribution of CB1-receptors in PFC of rats.

These experimental data suggest that endocannabinoid system in this brain area may play an important role in the continuity of homeostasis in cold stress.


Periaqueductal gray (PAG) is a midbrain structure closely involved in the stress-induced analgesia. It suppresses nociception by the descending efferent pathways to the dorsal horn of the spinal cord. Except stimulation of opioid receptors, the PAG is specialized to produce cannabinoid-mediated stress-induced analgesia. Attractive candidates for opiate modulators are neuropeptides from Tyr-MIF-1 family. These peptides also are involved in the development of stress. Based on behavioral and anatomical data about direct interactions of cannabinoid type 1 (CB1) receptors and μ-receptors in the PAG we decided to investigate the effects of the Tyr-W-MIF-1 neuropeptide on expression of CB1 immunoreactive neurons in rat’s PAG after immobilization stress. Light microscopic study was used to determine the distribution of CB1 receptor immunoreactivity. The obtained results showed that stress itself increased the expression of CB1 immunoreactive neurons in the PAG compared with intact animals, while Tyr-W-MIF-1 decreased stress-induced CB1 expression mentioned above probably by opioid/cannabinoid interaction. Further studies are needed to understand the exact role of Tyr-W-MIF-1 on CB1 receptors in response to immobilization stress.

Adjustability and steady health of the organism are reached by variable dynamic associations between the components of the organism. Imbalance of the process in the system results in rigidity, non-responsive or limited responsive system, which leads to increased morbidity and mortality. Heart rate variability (HRV) measurement evaluates the tonus and relation of sympathetic and parasympathetic part of the autonomic nervous system (ANS). Higher variability is indicator of better functional state of the organism. The aim of this study is the registration of homeopathic remedies' action over Autonomous Nervous System in patients with different clinical conditions by Heart rate variability test. The HRV measurements prove the immediate effect of homeopathic remedies over the physiological state of the organism and illustrate the changes on mental, emotional and physical level - the effect is 10 minutes after administration of the individually chosen remedy. Our experience from this work is very positive. For the homeopathic physician it is very rewarding to see that the remedy s/he prescribed registered its action over the system immediately and after long time. Patients feel more confident - they get visualization of the action of the remedy through modern scientific methods. HRV measurement is an additional indicator of the efficiency of the treatment and suitability of the remedy and can be used in fundamental research and in everyday practice of homeopathic physician.

19. Landzhov B., L. Malinova, Y. Kartelov, E. Dzhambazova. The cannabinoid 1 receptor antagonist AM251 alters the kyotorphin effect on density of CB1 immunopositive neurons in the amygdala. Compt Rend Acad Bulg Sci, 67(8), 1165-1170, 2014. IF=0.284

The endocannabinoid system is a modulatory system that has been strongly associated with the regulation of functions as learning and memory, pain perception and sensory physiology. Studies of the endocannabinoid system support its importance for multiple aspects of brain function. It is known that cannabinoid CB1 receptors are particularly concentrated in limbic structures such as the hippocampus and amygdala. There is also considerable evidence describing the common feature of opioid and cannabinoid receptor systems. Opioid-modulating peptides had been widely proved as the modulators of opioid functions. Literature data and our previous investigations showed that the short-chain opioid-like neuropeptide/neuromodulator kyotorphin (KTP) binds to a specific receptor and plays a role in pain regulation, thermoregulation, and exploratory behavior. It also alters the pattern of NADPH-d-reactive neurons in the hypothalamic paraventricular nucleus and striatum of Wistar rats. To our knowledge, no attention has been directed to the interaction between KTP and cannabinoid systems. Therefore, the objectives of the present study were
twofold: 1) to investigate the effect of KTP on density of CB1 immunopositive neurons in the amygdala of male Wistar rats; 2) to examine whether this effect is prevented by CB1 receptor antagonist AM251. Our results revealed that density of CB1 receptors was significantly increased in rats treated with KTP compared to the control. This effect was completely abolished by administration of AM251, which indicate the involvement of neuropeptide in the endocannabinoid signaling.


Clastrum is small and complex telencephalic structure. However there are still little data concerning its immunoreactivity. The aim of present study was to examine the presence, morphology, distribution and ultrastructure of NPY immunoreactive neurons and fibers in claustrum of the cat. Ten adult healthy cats from both sexes were used. All animals received humane care. They were anesthetized and transcardially perfused with fixative solution. Brains were removed, postfixed and cut. Slices were incubated with polyclonal anti NPY- antibodies according to standard Avidin-Biotin-Peroxidase Complex method adopted in Department of Anatomy and histology. NPY immunoreactive neurons and fibers were found throughout the entire extend from rostral to caudal of the dorsal claustrum. The neurons were classified according to their size into small (with diameter under 17 μm), medium-sized (with diameter from 18 to 24 μm) and large (with diameter over 25 μm). No specific pattern of distribution was found. Some of NPY-ir neurons were lightly-stained while others were darkly-stained. On the electron microscope level the immunoproducit was observed in neurons, dendrites and terminal boutons. Different types of NPY-ir neurons differ according to their ultrastructural features. Two types of NPY-ir synaptic boutons were found. No sex-related differences were found. As a conclusion we hope that the present study will contribute to a better understanding of the functioning of the claustrum in cat and that some of the data presented could be extrapolated to other mammals, including human.


Introduction. Induction of acute physical stress by low temperature or cold stress (CS) is
one of the most commonly employed animal models for studying different aspects related to stress. Considerable work has established the amygdala as a key site involved in the generation of fear, anxiety and emotional responses to external stimuli. Also its known that amygdala coordinates affective, autonomic, and behavioral responses. One of the mechanisms known to play a part in the response of an organism to stress is activation of the endogenous opioid system. Endogenous opioid peptides are substances which are produced in the body and take part in various functions as hormones or neuromodulators. The short-chain neuropeptide/neuromodulator kyotorphin (KTP) binds to a specific receptor and plays a role in pain regulation, thermoregulation and exploratory behavior. The mechanisms of its action are due to Met-enkephalin release and involvement of monoaminergic neurotransmitter systems. The aim of our study was to examine the effect of CS and KTP on density of CB1 receptors in the amygdala. Immunocytochemistry and morphometric analysis were used to determine density of CB1-immunopositive neurons in the amygdala of male Wistar rats exposed to acute CS (1 hour, on 4°C) and after intraperitoneal KTP injection. Data analysis revealed that CS and KTP applied alone significantly increased the density of CB1-immunopositive neurons in the rat amygdala. The quantity of immunoreactive cells in the rats, undergoing CS, demonstrated around 40% higher density of CB1-receptors compared with control group. The same effect was observed in group of rats injected with the neuropeptide, while the combination of both factors - CS immediately followed by KTP injection resulted in more pronounced (about 50%) increasing number of CB1-immunopositive neurons. Our findings revealed that alternation in CB1 receptor density occurs in response to cold exposure as well as KTP injection, but the effect of both combined factors was stronger. We could suggest that activation of endocannabinoid system is one of the mechanisms by which stress and neuropeptides affect the synaptic connectivity between amygdaloid nuclei and lead to modulation of emotional behavior, learning, and stress-response.


According literature data the animal’s response to stress depends not only upon the state and conditions of the animal but also upon the nature of the stressor itself. It is known that stress have wide-ranging effects on neuroendocrine, autonomic, immune, and hormonal function. Different research groups have shown induction of acute physical stress by low temperature exposure which have been reported to impair motor activity, modulate pain perception,
anxiety and depression-like behaviors in the animals. Considerable work has established the amygdaloid body as a key site involved in the generation of fear and anxiety responses, the assignment of emotional salience to external stimuli, the coordination of affective, autonomic, and behavioral responses. The aim of our study was to examine the effect of cold stress on density of CB1 receptors in the amygdaloid body. Immunocytochemistry and morphometric analysis were used to determine density of CB1 immunopositive neurons in the amygdaloid body of male Wistar rats exposed to acute cold stress. Our morphometric studies reveal that cold stress significantly increased (around 40 %) density of CB1 immunopositive neurons in the rat amygdaloid body compared with control group. Our results confirm that temperature fluctuation induces stress and endocannabinoid system is involved.


Pain transmission involves dynamic and interactive peripheral and central nervous system events and gonadal hormones have been demonstrated to interact with these systems at multiple levels. Estrogens have widespread effects throughout the CNS. Considerable evidence in the literature indicates that they modulate neural circuits known to participate in pain processes. The aim of our study was to investigate the effects of 17-β-estradiol on the pain latention of female rats during the period of prematurity. The experiments were carried out on immature female Wistar rats (90g). 17-β-estradiol was administered intraperitoneally once daily for 3 days of the experiment. The changes in the pain latency of the rats were evaluated using tail flick test 4 and 24 hours after injections. The obtained data show that 4 and 24 hours after injection 17-β-estradiol increased significantly TF latency during the whole period of the experiment. According to our data 17-β-estradiol takes part in the mechanisms of regulation of pain reaction of female immature rats. The effect of the gonadal steroid on pain perception cannot be fully explained by the known mechanisms at present. Further studies are needed to clarify the primary site and mechanism of these actions.

Endogenous gonadal steroids have many effects on the brain throughout the lifespan, beginning during gestation and continuing into senescence. There are data that they seem to play an important role in the open field behavior in adult rodents. The possible influence of the gonadal steroids on sex related determination of brain and behavior during the prematuration has received little attention in the literature. The purpose of the present study was to investigate the influences of 17-β-estradiol on the horizontal and vertical locomotor activity of immature female rats. The experiments were carried out on immature female Wistar rats (age 6 weeks, 90g). 17-β-estradiol (40 μg/100 g b.w.) was administered intraperitoneally once daily for 3 days of the experiment. The changes in the locomotor activity of the rats were evaluated using open field test 4 and 24 hours after injections. The data received show that exogenous estrogenization of immature female rats (4 and 24 hours after treatment) causes decrease in the horizontal (ambulation) and vertical locomotor activity (rearing) in open field test. The obtained results confirmed that estradiol significantly modify open field behavioral responses of female rats during the period of prematuration.


Kyotorphin (KTP), an endogenous analgesic neuropeptide in the central nervous system, is considered to be a neurotransmitter or neuromodulator. D-kyotorphin (D-KTP) is a synthetic analogue of KTP. Both peptides bind to a specific receptor and induced Met-enkephalin release. Thus, the effects of both peptides fall into two clearly identifiable groups: the ones, mediated via opioid peptides, and the opioid peptide-independent ones. For a long time we have been interested in the neuromodulating properties of KTP and D-KTP in analgesia due to different types of stress. Our previous data showed that both peptides reduced stress-induced analgesia, which suggest that they may act as an anti-opioid peptides counteracting the effects of stress. During acute stress increased secretion of adrenocorticotropic hormone (ACTH) and corticosterone (CORT) plays a key regulatory role on the basal activity of the hypothalamic-pituitary-adrenal axis and on the termination of the stress response. The aim of this study was to compare changes in ACTH and CORT concentration after various stressors, as well as after injection of KTP or D-KTP. The male Wistar rats were injected with KTP or D-KTP immediately after exposure of acute immobilization, cold and heat stresses. After decapitation plasma ACTH and CORT were assayed by a double antibody radioimmunoassay method. The various stressors applied seem to induce a different response of the HPA system as judged by quantitative changes in
ACTH and CORT release. In addition, this study points to KTP and its synthesized optical isomer D-KTP as a possible anti-stressor substances with potential clinical importance in the context of stress-related disorders, since they inhibited stress-induced elevations in two investigated hormones helping the organism to reach homeostatic level. Further studies are needed to understand the exact role of KTP in stress response.


Electromagnetic fields (EMFs) of extremely low-frequency range are widely used in therapeutic medical applications. Proof of effectiveness has been demonstrated in numerous clinical applications where each treatment employs specific characteristics of frequency, modulation, and intensity to achieve its efficacy. Most profound clinical applications of extremely low-frequency electromagnetic field (ELF EMF) are related to bone repair, wound repair, inflammation, and pain management.


Angiotensin II (ANG II) is defined as stress-related neuropeptide, with a significant role in maintaining of blood pressure and water-salt balance but several studies showed that it participates also in stress-induced changes in nociception. We aimed to study the effects of ANG II and its selective AT1 and AT2 receptor antagonists on the restraint stress-induced changes in nociception. Visceral model writhing test was used in mice exposed to 2 hours restraint stress (RS). Visceral pain reactions (writhes) were induced by intraperitoneally injected 1 % acetic acid. ANG II, AT1 receptor antagonist losartan and AT2 receptor antagonist PD123319 were injected intracerebroventricularly. Exposure to acute RS decreased significantly the number of writhes. Injection of ANG II, AT1 receptor antagonist losartan or AT2 receptor antagonist PD123319 alone were not able to change stress-induced antinociception (SIA). The antinociceptive effect of RS was augmented significantly by ANG II only when AT2 receptors were blocked. These data supported the assumption that brain angiotensin receptors take a part in the processing of information from visceral nociceptors. In spite of significant role of AT2 receptors in the regulation of
nociception under normal condition, our data showed an impact of AT1 receptor activation on the nociception in stress conditions.


Melatonin is the major hormone that is synthesized and secreted from pineal gland, and it is widely accepted as an antioxidant and a regulator of the circadian rhythms. It is also widely used in treatment of sleep disorders related to disturbed circadian rhythms and as an antioxidant adjuvant. There are substantial data for antinociceptive effect of melatonin in experimental models. We aimed to study the impact of melatonin in modulation of nociception in rats subjected to acute immobilization stress and on diurnal variations of both normotensive and spontaneously hypertensive rats (SHRs). The experiments were performed on male young-adult Wistar and SHRs using an analgesimeter for multiple assessment of phasic pain. Melatonin was administered acute (100 mg/kg, subcutaneously), and chronically in drinking water (10 mg/kg b.w./day) for two months. The results showed that acute dose induced transient antinociception similarly to immobilisation stress, but the hormone has bidirectional effects on stress-induced antinociception. Normotensive rats possessed diurnal variations in nociception with lower pain threshold during the dark phase of the day, whereas SHRs showed a disturbed circadian pattern without aberrations of nociception. Chronic melatonin treatment increased the pain threshold during the dark phase in Wistar rats and equalized it with their daily values but did not affect the nociception of SHRs. Taken together our data showed that acute treatment with melatonin lightly modulated stress-induced antinociception and the chronic hormone treatment induced a phase-dependent antinociceptive effect in normotensive Wistar rats without affecting the disturbed circadian rhythm of nociception in SHRs.


During normal metabolism, the body produces unstable molecules, the most common of which are the reactive oxygen species (ROS). Increased number of ROS, called oxidative stress, is capable to damage cells. To be able to combat the adverse effects of free radicals,
human body triggers the massive production of different antioxidants or accelerates their intake from foods. Scientific studies have demonstrated that long intense exercise such as endurance training, may cause an overwhelming of body's antioxidant defenses, leading to excessive oxidative stress and harmful outcomes. On the other hand regular exercise in intensity and duration has a wide range of beneficial effects on the body, by producing healthy amounts of oxidative stress. Contrary to what is believed until now, oxidative stress is beneficial in small amounts. In fact it's essential, because prompts the body cells to become stronger over time by increasing antioxidants and thus provide protection against potential injury or cellular damage. The beneficial consequences of regular exercise and harmful outcomes of exhaustive exercise due to amount of ROS production fit well with the concept of hormesis. It states that exposure to a low dose of a noxious or toxic agent can bring about results believed beneficial to the long-term welfare of the organisms. According to literature, physical inactivity combined with poor nutrition, excessive smoking and alcohol consumption leads to impairment in physiological functions and reduces the whole body resistance to oxidative stress, and can be regarded as one of the end points of the exercise associated hormesis curve. Moreover, it seems that physical inactivity through molecular pathways could facilitate the incidence of oxidative stress-related diseases. Therefore it seems that the human being is not designed to be inactive for survival.


Using the nicotinamide adenine dinucleotide phosphate-diaphorase (NADPH-d) reaction with nitroblue tetrazolium, we provided a detailed investigation of the distribution, dimensional characteristics and morphology of NADPH-d-positive neurons in the three main subdivisions of the human inferior colliculus (IC): central nucleus, pericentral nucleus, and external nucleus. In accordance with their perikaryal diameter, dendritic and axonal morphology, these neurons were categorized as large (averaging up to 45 μm in diameter), medium (20-30 μm), small (13-16 μm) and very small (7-10 μm). Their morphological differences could contribute to varying functionality and processing capacity. Our results support the hypothesis that large and medium NADPH-d-positive cells represent projection neurons, while the small cells correspond to interneurons. Heretofore, the very small NADPH-d-positive neurons have not been described in any species. Their functions - and if they are indeed the smallest neurons in the IC of humans - remain to be
clarified. Owing to their location, we posit that they are interneurons that connect the large NADPH-d-positive neurons and thereby serve as an anatomical substrate for information exchange and processing before feeding forward to higher brain centers. Our results also suggest that the broad distribution of nitric oxide (NO) synthesis in the human IC is closely tied to the neuromodulatory action of NO on collicular neurotransmitters such as GABA and glutamate, and to calcium-binding proteins such as parvalbumin. A deeper understanding of the relationship between NADPH-d-positive fibers in all IC connections and their colocalization with other neurotransmitters and calcium-binding proteins will assist in better defining the function of NO in the context of its interplay with the cerebral cortex, the sequelae of the aging process and neurodegenerative disorders.


Pain is the most common presenting complaint seen by physicians. The experience of pain is more than a simple sensory process. Pain is the result of a complex interplay between signalling systems, modulation from higher centres, emotional states, higher order mental processes and the unique perception of the individual. This article gives a relatively broad overview of the anatomy and physiology of pain. The normal pain pathways are described in some detail in a systematic fashion from nociceptor to central nervous system and back to periphery. Some of the mechanisms involved with pain transmission are also discussed and explained.


We compared the distribution, density and morphological characteristics of nitric oxide synthase-immunoreactive neurons (NOS-ir) in the rat and human claustrum. These neurons were categorized by diameter into three main types: large, medium and small. In the human claustrum, large neurons ranged from 26 to 40 μm in diameter, medium neurons from 20 to 25 μm and small neurons from 13 to 19 μm. In the rat claustrum, large neurons ranged from 19 to 23 μm in diameter, medium neurons from 15 to 18 μm and small neurons from 10 to 14 μm. The cell bodies of large and medium neurons varied broadly in shape - multipolar, elliptical, bipolar and irregular, consistent with a projection neuron phenotype. The small
neurons were most seen as being oval or elliptical in shape, resembling an interneuron phenotype. Based on a quantitative comparison of their dendritic characteristics, the NOS-ir neurons of humans and rats displayed a statistically significant difference.


Alzheimer's disease (AD) is a widespread neurodegenerative disease associated with a progressive loss of memory, which occurs after prolonged pre-symptomatic phase. In the process of searching for new biomarkers for early diagnosis of the disease, it was found reduced levels of endogenous dipeptide kyotorphin (KTP) in the cerebrospinal fluid of people suffering from AD, which is accompanied by increased content of phosphorylated tau protein. Our hypothesis is that the KTP plays a role in the pathophysiology of the AD in the related brain structures and behavioral alterations. We used intracerebroventricular (ICV) injection of streptozotocin (STZ) in rats as a model of sporadic AD. KTP was injected ICV for 14 days (7 days before and 7 days after STZ). Open field test was used for study the motor activity, exploration and anxiety and Novel object recognition test for study the working memory. Routine Congo red staining was performed to check Aβ amyloid deposits in the hippocampus and blood vessels. One month after the injection of STZ, rats showed hyperactivity, increased exploratory behavior, decreased level of anxiety and impaired working memory accompanied with Aβ amyloid accumulation in the hippocampus and brain blood vessels. Treatment with KTP diminished exploratoration and anxiety to the control levels and ameliorated memory deficit without changing of AD-induced hyperactivity and Aβ amyloid deposits in the hippocampus and blood vessels. This data showed slight but significant protective effect of intracerebral KTP against AD-induced behavioral abnormalities.
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