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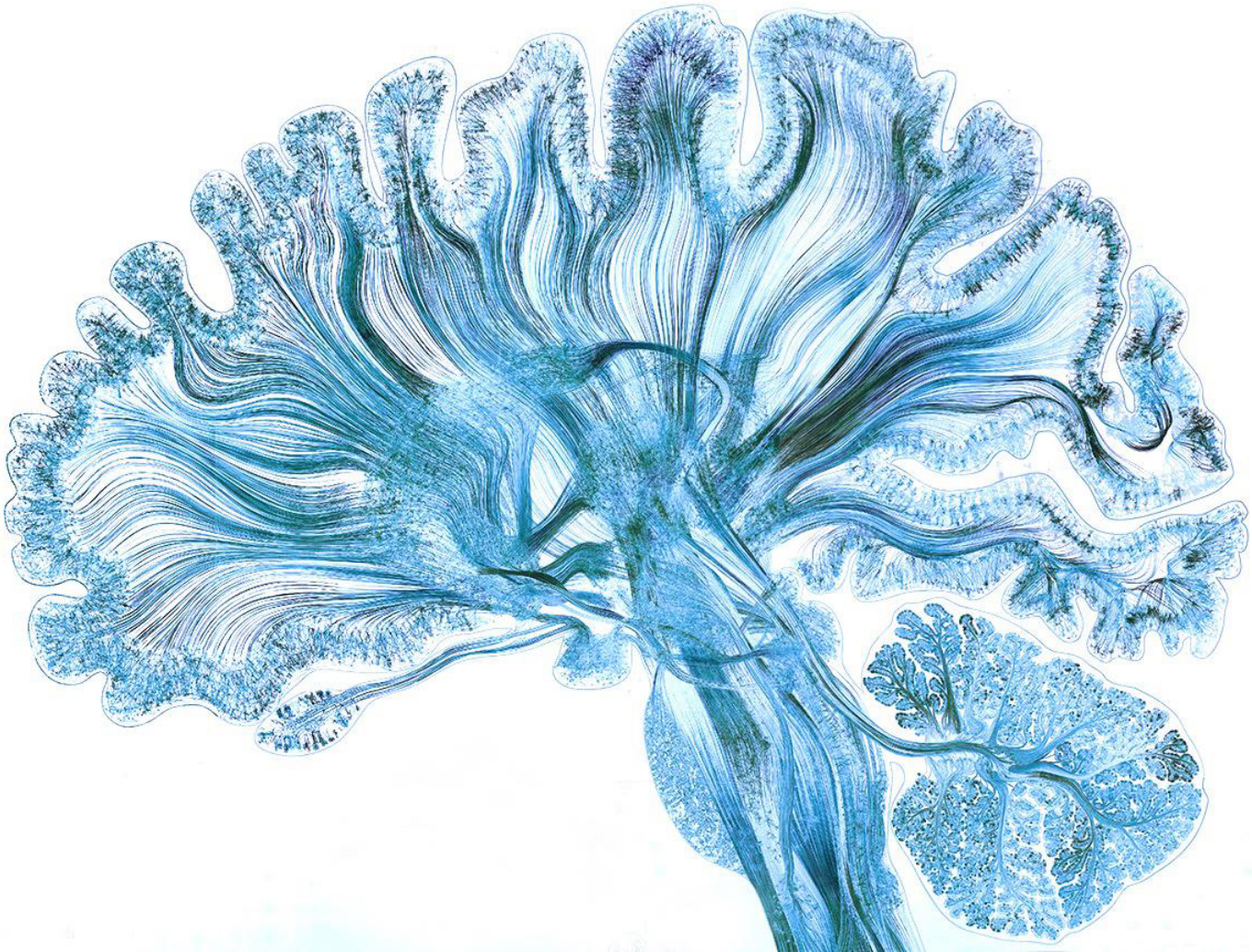
ABSTRACT BOOK

KNJIGA SAŽETAKA



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Acute restraint stress promotes anxiety-like behaviour and changes excitability of the central nervous system

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Introduction: Response to stress exposure has been identified as one of the risk factors for developing anxiety-like and depressive behaviour. While majority of studies indicate anxiogenic effect of acute stress, others imply its vital role in evolutionary adaptation. Possible mechanisms underlying the susceptibility to stress-provoked anxiety are inflammation, hippocampal neurogenesis, changes in gene and protein expression. Moreover, some researches imply protective effect of acute stress on animal seizure models by activating endogenous opioids and NO. Therefore, the aim of our study was to determine the influence of acute restraint stress (ARS) on anxiety-like behaviour and behavioural characteristics of lindane-induced seizures.
Methods: Adult male Wistar rats have been divided into control (C) and ARS group. Rats were stressed in restraining device for 1h prior to behavioural testing. After 20 min of rest, locomotor and exploratory activity have been registered in automated Open Field chamber. Independent measures included total ambulation distance and time, centre ambulation distance and time, time in the centre, and number of rearings. Afterwards, convulsions were induced by i.p. administration of lindane and seizure behaviour was evaluated. Seizure behaviour was assessed by incidence, seizure latency and the seizure severity.
Results: ARS significantly decreased total ambulation distance and time ($p<0.05$), and time in the centre ($p<0.05$) while the number of rearings was not significantly different between the groups. Furthermore, latency to seizures and duration of ictal periods was significantly different in ARS compared to the C group.
Conclusion: Our results strongly indicate that ARS protocol induces anxiety-like behaviour and changes the excitability of the CNS in male rats.
Key words: Stress, Anxiety, Epilepsy, Lindane, Seizure,

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Effects of lithium on noradrenergic turnover in the prefrontal cortex of chronically stressed rats

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Chronic stress can provoke depressive-like behaviors in rats. In pathophysiology of mood disorders lithium is known as an effective drug in the long-term stabilization of moods. It is known that depressive disorder is caused by insufficient signaling by monoamines, particularly noradrenaline (NA). Because of the significant role of NA in regulation of numerous brain functions in stress conditions, monitoring the changes of noradrenergic turnover in the prefrontal cortex (PFC) in chronically stressed rats treated with lithium may be very important in research of lithium role in reduction of functional deficiency of NA in pathological conditions. Therefore, in this study we examined: levels of enzymes involved in NA reuptake (noradrenaline transporter-NET), storage (vesicular monoamine transporters-VMAT2) and degradation (monoamine oxidase-MAO and catechol-O-methyltransferase-COMT), as well as concentrations of NA in the PFC of chronically stressed rats treated with lithium. An additional aim of the study was to test the behavior of chronically stressed rats treated with lithium. The investigated parameters were quantified by Western blot analyses and assay of enzyme activitie. We found that lithium treatment decreased high protein levels of NET and VMAT2, as well as the enzyme activity of MAO A in chronically stressed rats to the level found in unstressed animals. In addition, lithium treatment decreased concentration of NA and immobility of animals with depressive-like behavior. In conclusion, modulation of noradrenergic turnover in the prefrontal cortex of chronically stressed rats by lithium reduced functional deficiency of NA and stabilized behavior in animals with depressive-like behavior.
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In silico reconstruction of human dopamine transporter and design of novel neuroprotective drugs for Parkinson's disease

1ST PRIZE

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Abnormally folded alpha-synuclein protein, dysfunctional mitochondria, increased oxidative stress and reduced dopamine neurotransmitter synthesis are a
ll extremely well characterized phenomena in Parkinson's disease (PD) and are thought to be interconnected. While direct targeting of these areas has demonstrated neuroprotection *in vitro* and *in vivo*, there has been a major lack of success in clinical trials. A critical component in the failure of these clinical trials is the inability to specifically target drugs to dopamine producing neurons in the brain.
New drugs targeting the dopaminergic neurons by specific uptake through the human dopamine transporter (hDAT) could represent a viable strategy for establishing selective neuroprotection. Molecules able to increase the bioactive amount of extracellular dopamine, thereby enhancing and compensating a loss of dopaminergic neurotransmission, and to exert neuroprotective response because of their accumulation in the cytoplasm, are required.
By means of homology modeling, molecular docking and molecular dynamics simulations, we have generated 3D structure models of hDAT in complex with substrate and inhibitors. Our results clearly reveal differences in binding kinetics of these compounds to the hDAT in the open and closed conformations, critical for future drug design. The established *in silico* approach allowed the identification of three promising substrate compounds that were subsequently analyzed for their efficiency in inhibiting hDAT-dependent fluorescent substrate uptake, through *in vitro* live cell imaging experiments. Taken together, our work presents the first implementation of a combined *in silico/in vitro*-approach enabling the selection of promising dopaminergic neuron specific substrates.

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Identification of potential dual histamine H_3 receptor antagonist and serotonin reuptake inhibitors through ligand-based and structure-based approaches

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The major depressive disorder (MDD), routinely treated with selective serotonin reuptake inhibitors (SSRIs), is the second leading cause of disability worldwide. However, the treatment of MDD is complicated by high prevalence of residual symptoms connected to increased risk of relapse. Some of the most common residual symptoms are cognitive dysfunction and fatigue. Histamine H_3 receptor (H_3R) antagonists are both, pro-cognitive and wake-promoting agents. In pre-clinical study it was suggested that dual histamine H_3R antagonist and SSRI may have utility as a more efficient antidepressant therapy. The aim of this *in silico* study was identification of novel dual SSRI/H_3R antagonist using ligand-based and structure-based drug design techniques. Starting from structures and activities of known dual ligands, two GRIND-based 3D-QSAR models have been developed, SERT model (R^2 = 0.97; Q^2 = 0.79; SDEP= 0.124) and H_3R model (R^2 = 0.86; Q^2 = 0.75; SDEP= 0.184), and 3D-pharmacophores were constructed. Further, homology model of H_3R was built and refined with molecular dynamics. The hypotheses of binding modes for dual ligands were generated with molecular docking on H_3R model and X-ray structure of SERT. In the second part of this study, ligand-based and structure-based virtual screening models were generated and validated. Prospective screening of ZINC database was performed in order to extract novel chemotypes of dual ligands. Final selection of ligands was performed based on generated pharmacophore and docking models as well as predicted pharmacokinetic properties. Few novel compounds were emphasized as promising starting point for development of new classes of dual antidepressants.

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Structure and ligand based drug design strategies in the development of novel serotonin 5-HTt$_{2a}$ receptor antagonists

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The serotonin 5-HT_{2A} receptors are widely distributed throughout the central and the peripheral nervous system where they play a key role in many physiological functions. Abnormal activity of 5-HT_{2A} receptors is associated with various neurological disorders, such as depression, schizophrenia, anxiety, and Parkinson disease. In order to analyze 3D-structure of the