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tytuł pracy: ***Kompensacja stresogennych deficytów pamieci w wyniku blokady ośrodkowych receptorów angiotensyny II typu 1***

SUMMARY

Psychological stress is a preceding and causative factor for reactive mental disorders. It also leads to symptomatic aggravation of all the other pathological mental states, with emphasis on cognitive impairment. Evaluation of the burden of illness (Global Burden of Disease – WHO) indicates psychiatric disorders as the world's leading cause of disability, with economic burden of illness exceeding costs of cardiac and cancer care combined. This is caused by limited effects of the current psychopharmacological treatment on reduction of prevalence or disability of major mental disorders. Standard pharmacological treatment approaches in psychiatry are purely symptomatic, not causal. It should be emphasized that no casual and clinically effective anti-stress therapeutic strategy has yet been found. To fill this therapeutic gap particular attention was paid to Angiotensin II (AII) Receptor Blockers (ARBs, also known as sartans). The existence of central Renin-Angiotensin System (RAS), which functions goes beyond cardiovascular regulation, is widely recognized. Angiotensin II (AII) alongside cortisol (corticosterone in rats) is a major stress hormone which regulates: 1) the sympathetic nervous system activity; 2) the hypothalamic–pituitary–adrenal axis; 3) Dopaminergic, serotoninergic and cholinergic neurotransmission in brain. Moreover, mechanism of receptor interactions of sartans include not only AII type 1 receptor (AT_1R) blockade, but also peroxisome proliferator – activated receptor-gamma (PPARγ) activation, which results in reduction in rates of apoptosis, amplification of neural differentiation and inhibition of neuroinflammation (reduction of microglia and macrophage accumulation, inhibition of pro-inflammatory enzymes – COX2 / iNOS). For these reasons pharmacological actions of of telmisartan (TLM), the most lipophilic and the most potent PPARγ agonist among ARBs, were suggested as a beneficial anti-stress therapeutic intervention. Therefore, in the first research study, being a part of this PhD dissertation, the effects of chronic stress and TLM treatment on recall of aversively and appetitively motivated rats, have been assessed. Additionally, in the second study, we aimed to find whether TLM reduces stress-related memory decline in spatial hippocampal dependent learning tasks conditioned upon differences in level of stress induced by aversive nature of memory tests. Finally, in the third

study, we attempted differentiate the involvement of AT_1R blockade and PPARγ activation in neuroprotection provided by TLM.

The experiments were conducted on male Wistar rats (WAG/Amk). In the first study, the preventive action of long-lasting treatment with TLM (nonhypotensive dose of 1 mg/kg body weight daily for 21 days) against impairment caused by chronic stress (immobilization for 2 h daily / 21 days) on recall was evaluated in a passive avoidance (PA) situation and object recognition test (ORT). Locomotor activity and anxiety behavior were tested respectively, in an open field (OF) and an elevated plus-maze (EPM). In the second study chronic stress and TLM treatment were followed by three special learning and memory paradigms: Morris water maze (MWM), radial arm maze (RAM) and Barnes maze (BM). In the third study chronic stress with simultaneous oral administration of TLM (1 mg/kg), GW9662 – PPARγ receptor antagonist (0.5 mg/kg), or both in combination, were followed by a battery of behavioral tests (OF, EPM, PA, ORT), ELISA quantitative determination of serum corticosterone (CORT) and RT PCR evaluation of brain-derived neurotrophic factor (BDNF) gene expression in the medial prefrontal cortex (mPFC) and hippocampus (HIP).

TLM treatment diminished deleterious effects of chronic restraint stress on hippocampal and non-hippocampal memory, without alterations of locomotor activity and level of anxiety. This protective effect was more pronounced in aversive (PA) and stressful spatial tasks (MWM, RAM). In stressed subjects, TLM reduced CORT levels, normalized BDNF expression in HIP and increased BDNF expression in mPFC , in statistically significant manner. Those effects sustained despite of GW9662 treatment, which indicates that anti-stress capacity of TLM results from AT_1R blockade. The obtained results confirm the legitimacy of conducting a clinical trial. It appears that TLM may constitute a new therapeutic option in a stress-related cognitive impairment.