SUMMARY

DESIGN, SYNTHESIS AND STUDY OF BIOLOGICAL ACTIVITY OF PEPTIDES WITH PRO-REGENERATING AND NEUROPROTECTIVE PROPERTIES

mgr Izabela Załuska

Regeneration, i.e. the rebirth of cells, tissues or organs as a result of traumatic or disease damage, is an extremely complex process and includes repair, equalization and adaptation processes. They are designed to minimize the effects of these disorders and adapt the body to function in new conditions. Phenomena such as regeneration, compensation and adaptation of the body play a key role in this process. The repair of damaged tissues requires the activation of cells within them, the synthesis of cytokines enabling communication between cells and their interactions with the components of the extracellular matrix ECM (extracellular matrix), as well as the synthesis of enzymes enabling the degradation of damaged ECM components. In the last stage of healing, activated cells synthesize proteins necessary for the reconstruction of damaged tissue and enzymes involved in its reconstruction.

The goal of pharmacological stimulation of regeneration is to stimulate the body's ability to regenerate. Numerous groups of chemical compounds activate a number of metabolic processes in the body. The concept of "self-repair" of the system induced by small molecule compounds seems to be a simple and quick solution to the body's limited regenerative capabilities. This action may increase the activation of progenitor cells, i.e. tissue-specific stem cells in repairing tissue and organ damage.

Changes in brain tissue caused by ischemia (stroke) lead to the death of neurons, which causes impairment of brain function (in extreme cases to death), as well as other body systems controlled by it (e.g. the motor system). These changes become irreversible after a few hours. Compounds with neuroprotective properties that are able to reverse the negative impact of stroke-related biochemical factors on brain cells (mainly neurons) are currently sought after. In neuro-damage diseases, a whole series of simultaneous or successive processes occur that directly or indirectly result in the death of nerve cells. Dysregulation of biochemical and electrochemical processes caused by damage manifests itself in energy deprivation, oxidative stress and acidosis, and in general leads to excitotoxicity. Among the most promising candidates are basic CPP class peptides and their alanine analogues, as well as peptides containing the RGD motif.

In my work, I undertook to design and research peptides with pro-regenerative and neuroprotective properties. Peptides with potential pro-regenerative activity are AGF9 peptide, which has a characteristic RGD motif, corresponding to, among others for cell adhesion processes associated with remodeling during tissue differentiation. For research on skin regeneration processes, I also designed AGF9 peptide analogues, including AGF27 peptide, the N- and C-terminal extension of the AGF9 peptide fragment, as well as a series of RGD peptides with a multiplied sequence to check if the RGD motif is responsible for the potential regenerative properties of the AGF9 peptide. In cooperation with the Medical University of Gdańsk, the peptides were subjected to biological tests, i.e. cytotoxicity, proliferation of keratinocytes and fibroblasts, migration and chemotaxis of skin cells after stimulation with compounds obtained by me.

Another goal of my work was to design and study peptides with neuroprotective properties. For in vitro studies of neuroprotective and anti-damage efficacy I chose, among others a series of peptides and analogues with the RGD motif, CPP peptides such as Tat (49-57) -NH2 (arginine-rich motif rich ARF), which is a fragment of the basic protein Tat HIV-1 and its less basic PTD4 analogue . In this way, I examined the correlation between the structure and neuroprotective activity of the Tat (49-57) -NH2 peptide, which until now has been combined with a large number of arginine residues in the sequence. In my work, I checked the effect of the multiplied RGD sequence on neuroprotective properties in a multifactorial model of neurological damage. Cultures of hippocampal neurons were used in the study, and excitotoxicity (glutamic acid, NMDA, kainic acid), glucose deficiency, acidification of pH 6.35 were used as stressors, and synthesized peptides were used as neuroprotective agents. Peptides from the RGD series showed protective properties against individual factors and did not show significant toxicity in the tested model.

The results obtained in this dissertation are interdisciplinary and constitute the basis for research on finding compounds that stimulate the skin regeneration process and on the prevention and treatment of stroke effects.