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„ANALYSIS AND EVALUATION OF THE EFFECTIVENESS OF ANOREXIC AND SAFETY PROPERTIES FOF THE NEW HISTAMINE H3 RECEPTOR LIGANDS"

Obesity is one of the major health problems of 21st century. World Health Organization (WHO) estimates, that ca. 30-80% of adults, and even up to 30% kids and adolescents might be afflicted. Therefore, succesful obesity treament became one of the nowadays top healthcare topics. Moreover, WHO declared obesity as an 21st century epidemic. Obese individuals appear more prone to cardiovascular diseases: ischemic heart disease, hypertension, and diabetes, diseases of the digestive system: gallstone disease, nonalcoholic fatty liver disease and increased risk of developing: colorectal, gallbladder, pancreas and kidneys cancers. This shows the importance of conducting research leading to obesity-reduction connected drug discovery. Paying attention to a still growing number of obese people, associated with increased incidence of this condition with many „side" diseases as well as of serious complications, the search for effective and safe drug with anorectic properties is entirely justified and needed. Studies seeking new paths for treatment of obesity resulting in novel, effective and safe compounds that may be future weight-loss medicines can certainly bring tangible social and economic benefits.

Amongst all, one of novel approaches is to search for novel anorectic compounds that might influence the frequence of food intake. Among others, the use of histamine H_3 receptor ligands in treatment of diseases such as obesity has been postulated. Since the stimulating effect of increased histamine released in Central Nervous System on food intake (through eg.: appetite reduction, white adipose tissue lipolysis increment - the process of fats disintegration and increment of motor activity) had been discovered.

Potential drugs that might increase central histamine levels, and thus reduce weight by inhibiting appetite could be found in the group of compounds that inhibit histamine H_3 receptors activity. This might lead to increased levels of histamine, that acts through histamine H_1 receptors and participates in leptin-dependent (a hormone produced mainly in white adipose tissue) food intake inhibition. Moreover, histamine regulates (through H_3 heteroreceptors), levels of other neurotransmitters, such as acetylcholine, norepinephrine, dopamine, and thus controls food intake and locomotor activity. Histamine also affects the peripheral metabolism by increasing white adipose tissue lipolysis.

Therefore the aim of this study is to synthesize and detemine potential anti-obesity properties on novel compounds – histamine H_3 receptor ligands. Further structure-activity analysis might help designing, and thus obtaining, novel and even more active and save compounds displaying such activity. The project assumes the examination of the influence of tens novel compounds, designed and obtained in Department of Technology and Biotechnology Of Drugs, Jagiellonian University Medical College. The term potential anorectic effects in rats fed a preferential feed (model of excessive eating ofwestern diet). These studies will also clarify the relationship between the strength of activity of the compounds, and their therapeutic efficacy in the proposed indication and severity of possible side effects. The results of preliminary studies for 3 of the chosen compounds, helped to confirm the validity of proposed research hypothesis. Proposed studies consider chemical synthesis as well as pharmacological studies (with possible toxicity exclusion).