

Insulin receptor sensitization improves affective pathology in various mouse models

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Valorization

Relevance for society

Diabetes and neuropsychiatric disorders are major health and economic burdens in the next decades. It is estimated that 9% of the world's adult population suffers from diabetes, and alarmingly, over 13% are obese and risking developing the disease, which accounts for 1.5 million direct deaths per year. In other hand, recent reports reveal that over 400 million adults suffer of depression and 47.5 million of elderly dementia, 60-70% directly linked to Alzheimer's disease, the most prevalent neuropsychiatric disorder, recently considered to be "brain diabetes" or a Type III diabetes.

Insulin resistance is the hallmark of diabetes and metabolic syndrome and has been associated with depression. Whereas depression increases the risk for diabetes, people with diabetes are twice as likely to experience depression when compared with the general population. A growing body of evidence in the later years and of the present work has enlightened the role of compromised brain insulin receptor signalling in the aetiology of neuropsychiatric disorders including depression.

Recently, several types of insulin receptor sensitizers have been offered as a potential remedies to tackle affective disturbances. Namely, several classes of pharmacologically active compounds have been developed lately. They include meglitinides and sulfonylureas, which increase a release of insulin by the beta islets in the pancreas; biguanides, which decreases liver gluconeogenesis and increases number of receptors recruited to the membrane and thiazolidinediones, which increase mitochondrial biogenesis and improve lipid metabolism.

Unfortunately, and albeit successful results from the application of these compounds as antidiabetic and even antidepressant agents, associated side effects may vary from

osteoporosis, cardiovascular complications, increase in body weight and food cravings, kidney failure, cancer, severe hypoglycaemia and other undesirable consequences.

In the present studies, dicholine succinate, an endogenous molecule, has been shown to elicit an antidepressant-like effect in the pre-clinical models of depressive-like state of various origins. This opens the possibilities to consider this substance as a candidate to additive pharmacotherapy of depression, in particular when this disorder is associated with metabolic syndrome. Also, it can be used during obesity as a food supplement to counteract negative effects of high amounts of dietary cholesterol and fat. It is expected that the use of dicholine succinate will be not accompanied by significant side effects that are known for the treatment with other insulin receptor sensitizers. The results in this thesis also support the view that dicholine succinate can be used during senile depression. It can be particularly useful for patients suffering from the combination of above listed syndromes that are often co-morbid. Thus, the application of dicholine succinate as a food supplement and as a drug can be of medical and economic importance.

Apart from a discovery of a potential of dicholine succinate being a candidate substance during several forms of affective pathology, our studies have contributed in the optimization and development of animal models of investigated syndromes. A model of affective pathology associated with dietary cholesterol challenge, was newly developed. Models of stress-induced and aging-related affective syndromes were optimized in terms of the use of labour and other resources. Finally, we validated oral ways of chronic dosing with antidepressants, which allows reducing costs for translational studies based on chronic dosing of animals, and significantly ameliorating animal welfare. We have probed and confirm the effectiveness of a delivery of drugs with food or drinking water, which could be particularly useful in future experiments with long protocols and on immunodeficient animals.

Target groups

In our studies, we have found beneficial effects of the applications for the insulin receptor sensitizer dicholine succinate as an antidepressant during stress, aging and metabolic conditions associated with consumption of Western-diet type of food. Therefore, we consider our target groups to be 1) patients with depression associated with obesity / metabolic syndrome, 2) patients suffering from elderly depression, with or without metabolic syndrome, 3) individuals with a risk of a development of obesity / metabolic syndrome. For the first two target groups, one can anticipate the usefulness of dicholine succinate as an adjustment therapy of depression that can increase the effect of main antidepressant treatment and allow to decrease its dose, thus, leading to a less pronounced side effects of a conventional drug.

As potential outlook of presented work, we foresee a potential interest of pharmaceutical companies to complete necessary tests and develop dicholine succinate as a formulation for pharmacotherapy of depression and associated symptoms, and / or a food supplement, like other endogenous molecules or elements (e.g., fluoride). It is likely that the use of dicholine succinate as a food supplement as for instance, would generally help to improve a public health. It is expected that the production of the compound will be relatively inexpensive and is also widely available for all parts of the population. Nowadays this could be especially important. Given the fact that a lifestyle in developed countries involves lots of stressful life events and the consumption of high-fat, salty and sweet foods is increasing, the use of dicholine succinate can be beneficial in the prevention of metabolic syndrome, obesity and associated with these disturbances depression. Also, a general tendency of a global population to age makes potential use of dicholine succinate a promising tool of prevention with pathological developments related to elderly.

From an economical point of view, filing of a patent for the use of dicholine succinate could be an option to go for. The use should be defined for conditions where dicholine succinate have shown its efficacy in pre-clinical models, such as depressive pathology associated with metabolic syndrome, senile depression and a risk of the development of these conditions.

Activity / Products

The major finding in my studies that is described in this dissertation is that the enhancement of insulin receptors by dicholine succinate protects mice from the deleterious effects of a development of affective symptoms during stress, during stress, aging and challenge with high amounts of dietary cholesterol. Also, dicholine succinate is increasing expression of genes related to neuronal plasticity and survival. As the models used have a high translational validity to what has been described in the human clinic, we hypothesize that patients could benefit from the similar properties of dicholine succinate as they are hereby described in pre-clinical experiments.

Innovation

The work hereby presented has been innovative in various regards. First, we have validated the induction of affective pathological disturbances, characterized by molecular and behavioural phenotypes, in mice models of stress-induced depression, using an optimized protocol that reduces labour and time costs (Chapter 2,3). Second, we have proposed a new model of affective changes that are resulting from a diet with high cholesterol content (Chapter 4 and 6). Third, we have validated the efficacy of chronic dosing with food and water of antidepressant drugs, that, we believe, greatly helps to optimise economic costs for experimental procedure that require such dosing, and contribute to the animal welfare. Finally, we have shown that insulin receptor signalling is a mechanism that is implicated in the affective changes

during exposure to a Western diet-like diet and that it can be targeted by insulin receptor sensitizers, such as dicholine succinate.

Implementation

In line with the abovementioned relevance for the scientific and medical communities, society and industry, the implementation of the knowledge generated in the current dissertation is also multidimensional, as already discussed. From an academic perspective, results have been or will be published in peer-reviewed international journals and presented at national and international conferences.