Modified swim test as a mouse depression paradigm of enhanced cognitive processing

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Valorization

Relevance for society

Major depression was projected to become the second most common cause of disability worldwide by the next decade. Depression as a major health issue is illustrated by its death-toll, which currently claims more lives per year than road-traffic accidents. At the same time, there is an obvious need for an improvement in the treatment of depression, as up to 45% of depressed patients do not show improved mood after advanced therapy and 15% of patients do not respond to any antidepressant therapies. Important features of depression are its link to stress response and exaggerated cognitive processing of negative experiences; the neurobiology of these phenomena, however, was not properly addressed in most of available animal models of this disorder. The complexity of the mechanisms of depression and a lack of reliable and effective methods of modeling depression in animals complicate the search for more effective treatments of this disorder.

As and outcome from our studies, we have offered a new model of depression, which can mimic behavioural and molecular signs of a depressive-like state, such as helpless behaviour and the over-expression of GSK3β, a molecular hub of distress/major depression in humans. This new mouse paradigm models a new aspect of depression that was not addressed so far in translational research with this condition, an enhanced contextual conditioning of adversity. In addition, our mouse model replicates an inter-individual variability in the susceptibility to depressive disorder and thus, can enable the studies of the neurobiology of distinct susceptibility to depressive syndrome that is rarely possible in pre-clinical modeling of depression.

Importantly, newly proposed modified swim test with delayed testing requires minimal experimental work (three sessions of 6 min each) that is highly relevant for animal welfare and labour costs. In comparison to basic models of depressive behaviours such as Porsolt test and tail suspension test, our model provides more refined way of modeling a depressive-like state in small rodents that is also highly economically effective. Other models of comparably high face and construct validity in modelling

depression, as for instance, chronic stress and learned helplessness paradigm, require extremely high labour and time costs and regarded as not optimal in terms of animals well-being. In general, we believe that the modified swim test may provide a methodological solution for combining the advantages of chronic models of depression, while overcoming their disadvantages of highly demanding resources they typically require, as well as improving laboratory animal welfare. Given listed above advantages of the model, we trust that this paradigm can be very useful in screening of new drug candidates against depression.

We believe that our studies that have identified antidepressant-like properties of thiamine and its highly bioavailable precursor benfotiamine that were not known before, support this view and demonstrate a power of new modified forced swim test. Our studies demonstrated that chronic applications for the thiamine (vitamin B1) and its precursor benfotiamine reduce molecular and behavioural changes associated with depression that suggests their use as supplementary therapy. Also, we found that the doses of imipramine which are much lower than commonly used concentrations of this antidepressant are efficient in preventing depressive-like changes. This can help to refine the dose of tricyclics in the clinical practice. Finally, our experiments with T2, previously regarded as inactive form pf thyroid hormone, revealed its antidepressant-like properties. Thus, T2 can be used to counteract depressive symptoms as well.

Target groups

We consider our target groups could be patients and individuals, who are genetically susceptible to develop depression or exert clinical depression, which is particularly associated with experience of traumatic events. Also, care takers who can suffer from their activities related to these individual can be considered as target groups.

Activity / Products

As potential outlook of presented work, we foresee a potential interest of pharmaceutical companies to complete necessary tests and develop thiamine alone with its precursors, and T2 hormone as formulations for

pharmacotherapy of depression and associated symptoms that would help to improve a public health.

In addition, in a course of the present Thesis we developed the modified paradigm that offers more effective and refined approach to address the role of enhanced cognitive processing in the pathophysiological mechanisms of depression. This can result in the identification of new targets of pharmacological management of depression and screen new candidates to antidepressant therapies more accurately and effectively.

Innovation

The work hereby presented has been innovative in various regards. First, we have established and validated a new mouse depression paradigm; so far, a few, if any analogues of it were reported in the literature. Second, with this paradigm, one can segregate susceptible versus resilient to depressive state animals at very low labour and time costs that was not possible earlier. Third, this is the first depression model that enables the tracking of the dynamics of molecular / neurobiological substrate of this condition in relation to the time of a trigger of a depressive-like state; no such paradigms were reported in the literature till now. Fourth, molecular and neuroanatomical substrates of enhanced contextual conditioning have been determined, such as an over-expression of GSK3β in the prefrontal cortex. Finally, T2 and thiamine (vitamin B1) were identified as new therapies of depressive state that was unknown before.

Implementation

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