Mini Review

Translational research of antidepressants with an example of cannabidiol effects

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Summary

Despite that not all symptoms of depression can be achieved in animals the translational animal models can mimic the aspects of human depressive disorders in terms of disease symptoms as well as their neurobiological mechanisms. Results of testing the antidepressant drug effects in behavioral animal models of depression are presented. In these models, depressive-like behavior is induced by various stress factors in laboratory animals. However, patients suffering from the Therapeutic Resistant Depression (TRD) do not have high-stress markers. Thus, animals with predisposing factors leading to heightened stress responsiveness as a tool for discovering drugs for human TRD treatment are also presented. Antidepressant treatment effects are reported to be achieved through complex influences on body responses associated to reward, stress, and inflammation, the processes reported to be influenced by activities of the Endocannabinoid System. Cannabidol (the cannabinoid without abuse potential) is reported as an antidepressant agent.

Introduction to translational research on depression

According to the definition of the "European Society for Translational Medicine (EUSTM)", translational medical research is defined as an interdisciplinary branch of the biomedical field supported by three main pillars: benchside, bedside, community [1].

The translational medical research relies on the principles of transformation of the basic research results into clinical medical practice. The phenotype of human disease is modeled in laboratory animals by identifying candidates for biomarkers enabling testing of pathways and networks, which could then be validated in clinical practice, even for the choice of appropriate treatment. In the case of preclinical studies on depressive disorders, it has to be admitting that despite that not all symptoms of depression can be achieved in animals the animal models used are still essential not only for testing and validating the effects of new drugs with potential antidepressant activity but also for improvement of our knowledge on neurobiology of this psychiatric disorder.

Symptoms of depressive disorders in man (- *persistent*

feelings of sadness, hopelessness, worthlessness, or emptiness; – irritability, frustration or restlessness; – loss of interest in activities or hobbies that used to be enjoyable; – difficulty sleeping, sleep disturbances, or sleeping too much; – fatigue and lack of energy; – difficult thinking, remembering, concentrating, or making decisions; – appetite or weight changes; – recurrent thoughts of death or suicide; – physical symptoms such as headaches, stomach aches, or back pain) are associated with behavioral changes. Thus for investigating antidepressant drug effects in rodent behavioral tests attention has to be paid to disinhibition of behavior suppressed by some means (often induced by stress) that can be monitored objectively while into account has to be taken specific endophenotypic behavioral variations [2]. However, the animal models of depression should correlate as much as possible with all other changes observed in depressed patients: a) maladaptation with increased irritability; b) neurochemical changes: disorders of aminergic neurotransmission; c) neuroendocrine disorders: elevated adrenal steroid levels; d) immune deficits. Although not all symptoms of human depression can be achieved in animals, the translational animal models of depression used are still useful to find new drugs with potential antidepressant activity and also to improve our knowledge on the neurobiology of this psychiatric disorder [2–7].

Animal models of depression

Historically, the following behavioral animal models of depression have been the most recommended:

1) "Mother-Infant Separation in rhesus monkeys" [8,9];

2) "Partner off Spoiling in monkeys" [9];

3) "Learned Helplessness in dogs or rats" who fail to escape inescapable electric shocks in a the situation when escape is possible (Maier and Seligman 1976);

4) "Forced Swim Test"; behavioral despair rats and mice; immobility is reduced by antidepressants [10];

5) "Tail Suspension Test" in mice; antidepressants reduce the duration of immobility [11];

6) "Repeated social defeat" in mice; antidepressants decrease signs of despair [4];

7) "Bilateral Olfactory Bulbectomy (OBX)" in rats or mice causing in animals behavioral, immune and aminergic neurotransmitter functioning alterations which correlate well with changes in depressed patients [12-14]. *E.G.* i*n our laboratory, we have proven that olfactory bulbectomized rats had: a) lower basal levels of DA and 5HT and their metabolites [15]; b) increased levels of GABA and glutamate; lower basal levels of DA and 5HT plus their metabolites; increased levels of GABA and glutamate; higher intravenous self-administration of methamphetamine); c) reduced levels of endocannabinoids [16].*

Endocannabinoid system and depression

The results of both preclinical and clinical studies on depression indicate insufficient neuromodulatory functions of the endocannabinoid system, and therefore attention is focused on the possible antidepressive effects of cannabinergic therapies [17-26].

The attention is often paid especially to assessing the possible antidepressant effects of cannabidiol CBD, the second major component in cannabis without the abuse potential [25,27-31].

Cannabidiol antidepressant potential

In our laboratory, we have registered improving effects of CBD on the alterations which are reported to be induced in the rat model of depression by Bilateral Olfactory Bulbectomy: a) hyperactivity in the Open field test (Klein & Brown, 1969); b) immune changes [13]; c) aminergic hormonal changes (Cairncross,1977). In our laboratory CBD treatment (5mg/kg/day, orally for 15 days) decreased both the hyperactivity of bulbectomized rats in the open field test and the suppression of the phagocyting activity of their leukocytes and also showed antidepressant-like effects in our ethopharmacological mouse behavioral model of depression: "Repeated Social Defeat in mice.

The number of scientific reports on possible CBD antidepressant effects was gradually increasing [17,20,32-38]. We have proven that in the rat model of depression our olfactory bulbectomized rats had: 1): reduced levels of endocannabinoids [16];

2): a) lower basal levels of DA and 5HT and their metabolites; b) increased levels of GABA and glutamate; c) showed higher intravenous self-administration of methamphetamine . CBD was also reported to facilitate neurogenesis what helps to attenuate besides psychotic-like and anxiety-like behaviors also depressive-like behavior [39].

In the cross-sectional Clinical Study on cannabidiol in human users [40] almost 62% of participants reported CBD using as a specific therapy for depression, anxiety, pain, and sleep disorders. A promising therapeutic profile for cannabidiol as an antidepressant drug brought reports of its influence on cellular and molecular changes in brain regions related to the neurobiology of depression: a) increases in levels of BDNF (="peripheral biomarkers" of the Therapeutic Resistant Depression – [41,42]; b) increased synaptogenesis in the medial prefrontal cortex with increases of neurogenesis in the hippocampus [24].

Reviews recently available presenting the therapeutic potential of cannabidiol state the following possible indications: anxiety disorders, post-traumatic stress disorder, autism spectrum disorders, epilepsy, psychotic disorders, Parkinson disease, Alzheimer disease; and depression [21,23,43-45].

Animal models and potential treatment of Therapeutic Resistant Depression (TRD)

Not all signs and symptoms of depression in man respond to the antidepressant treatments. About 60% of patients with Major Depressive Disorder (MDD) do not respond sufficiently to the initial antidepressant treatment. Such condition is described in clinical psychiatry as the Treatment-Resistant Depression (TRD).

The diagnosis, epidemiology, and underlying biological mechanisms, as well as new treatment modalities for TRD, were for instance the topics of the "International Thematic Meeting of the College of Neuropsychopharmacology (CINP)" held in Prague, the Czech Republic in 2017. The main topics discussed (understanding the mechanisms underlying the pathophysiology of human TRD and also finding translational animal models that could mimic the whole pathological complexity of TRD) might be a key to identifying new therapeutic approaches [46,47].

The animals defined to be suitable for TRD modeling in preclinical translational research should show increased sensitivity to stress; resistance to chronic treatment with conventional antidepressants; good response to novel modes of antidepressant treatment, e.g. ketamine and deep brain stimulation. As the most promising models are mentioned: a) Rat strain Wistar-Kyoto (WKY); b) Congenital learned helplessness (cLH) rat strain; c) High anxiety behavior (HAB) mouse strain; d) OCT2 ("Organic Cation Transporter

for NE; 5-HT") null mutant mouse strains e) CB1 receptor knockout mice [5,6,48-50]. Repetitive high-frequency transcranial magnetic stimulation reversed depressive-like behavior and protein expression at hippocampal synapses in chronic unpredictable stress-treated WKY rats by enhancing Endocannabinoid Signaling [51-53], and cannabinoid cannabidiol elicited antidepressant-like effects in both sexes of Wistar-Kyoto rats [54-59].

Summary

The presented behavioral animal models of human depression prove their importance in searching for effective antidepressants. For fully successful translational research of the pathophysiology and treatment of human depressions (including TRD), it will be important (if technical options are available) to focus, already in the preclinical phase, not only on behavioral markers but also on identificationg possible dysfunctions or lesions of brain structures and their correlation with clinical findings in patients with these types of disorders.

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