Краткие сообщения

DOI: 10.14529/hsm160409

NEURONAL MECHANISMS OF THE BENEFICIAL MOOD EFFECTS OF PHYSICAL EXCERCISE

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Aim. The current work aims to summarize the experimental data (from author's and other laboratories) on the neuronal mechanism of the mood effect of physical exercise and to suggest a potential mood-stabilizing mechanism of physical activity. **Materials and Methods.** Physical Depression is a brain disorder characterized by severe emotional, cognitive, neuroendocrine, and somatic dysfunctions. Based on this concept, the author performed a review of experimental data on various ways to manage depression including medical treatment and physical exercise. **Results.** Although the last generation of antidepressant drugs demonstrates improved clinical efficacy and safety, the onset of their clinical effect is still significantly delayed from the beginning of the treatment course, and significant number of patients show lack of adequate response to these drugs and/or relapse of the disease even after initially successful treatment. Certain non-pharmaceutical strategies are used as adjuncts or replacements to antidepressant drugs when the formers are ineffective. One of such strategies is the voluntary physical exercise. **Conclusions.** Voluntary physical exercise can be an adjunct physiotherapeutic treatment in depression, given together with the pharmacotherapy, e.g., with SSRIs. One of the potential mechanisms of action of physical exercise in depression is stimulation of basic and/or reversal of the SSRI-induced inhibition of 5-HT tone. Other potential mechanisms, such as neuropeptide pathways, should be investigated in the future studies.

Keywords: *depression, antidepressant drugs, voluntary physical exercise, serotonin, norepinephrine, dopamine, neuropeptides, β-endorphin, oxytocin, vasopressin.*

Introduction. Usually the word "depression" refers to the major depressive disorder (MDD). According to the Diagnostic and Statistical Manual (DSM), MDD can be diagnosed when two major symptoms (depressed mood and anhedonia, or inability to feel pleasure) and two more symptoms out of eight (decreased self-esteem, feeling of guilt, impaired memory and concentration abilities, increased fear and anxiety, insomnia or hypersomnia, increased or decreased appetite, general retardation or agitation, and repeated thinking about the death with or without suicidal plans) are present for at least two weeks (American Psychiatric Association, American Psychiatric Association [1]. Depression affects, at least once in a lifetime, at least twenty percent of the general population. It has higher prevalence in females than in males, but is not linked to the geographical location, race, and ethnicity, socioeconomic or cultural background [2]. Depression is associated with a high risk of suicide and increased mortality from comorbid somatic (usually cardiovascular) disorders. Generally, somatic disorders comorbid with depression are characterized by a more severe course and worse prognosis. Depression can also be comorbid with an increased risk of other mental disorders, such as generalized anxiety (GED), panic disorder and substance and alcohol abuse. As a result, depression is a second major reason for disability in the industrial countries. It is estimated to become second major reason for disability world-wide by 2020 [2].

Materials and Methods. There are several lines of evidence that the depression is a complex organic disease rather than simple mood perturbation. First, pharmacotherapy of depression (alone or in combination with psychotherapy) shows higher efficacy than the sole psychotherapeutic treatment [10, 22, 29].

Second, there are physical symptoms associated with depression, such as dizziness, headaches, chronic lower back pain, gastro-enteral (abdominal pain, constipation or diarrhea) and endocrine (usually thyroid hypo- or hyperfunction) abnormalities, and irregular and/or painful menstruation cycle [3, 4].

Third, depression can be induced by a phar-

macological intervention, such as administration of reserpine, an inhibitor of the vesicular monoamine transporters (VMAT) [34] or by a special diet, such as tryptophan-depletion [11].

Fourth, there are structural and functional CNS abnormalities associated with depression. These abnormalities usually occur in the limbic system of the brain, which is responsible for the emotional processing, stress response, and memory formation and acquisition [28].

There are pharmaceutical and non-pharmaceutical treatment strategies for depression. The first line pharmaceutical treatment for depression is selective 5-HT reuptake inhibitors (SSRIs) [30].

Results and Discussion. SSRIs increase 5-HT availability via its reuptake inhibition. Serotonin is a brain neurotransmitter which plays an important role in the regulation of mood, emotions, sleep, sexual and eating behavior and is involved in pathophysiology of depression [44].

The last-generation SSRIs demonstrate relatively high safety and efficacy; however, only about one third of patients with the MDD achieve complete remission after a chronic treatment with SSRIs. One third of patients demonstrate only partial relief of the symptoms and the last third show no response to the treatment [30, 41].

It was suggested that the lack of adequate response to the SSRIs, at least in some patients, may be explained by the 5-HT-induced suppression of catecholamine (norepinephrine: NE and dopamine: DA) neurotransmission [13, 14].

Indeed, an increase in 5-HT tone leads to the inhibition of NE and DA neuronal firing activity. This effect is mediated via 5-HT2A and 5-HT2C receptors, respectively. Catecholamines play an important role in reward, drive, and motivation. Therefore, inhibition of catecholamine transmission can contribute to depressive symptoms, such as anhedonia and fatigue [8, 14, 17].

Several strategies are used to prevent inhibition of NE and DA tone and to achieve better outcome of the treatment. One of these strategies is replacement of SSRIs by dual 5-HT/NE (SNRIs) or triple 5-HT/NE/DA reuptake inhibitors (TRAs) [18, 19].

Another strategy is co-administration of SSRIs with various antagonists of 5-HT1A/1B (to prevent auto-inhibition of 5-HT neurons), 5-HT2A/2C (to prevent the inhibitory effect of 5-HT on NE and DA neurons, respectively) and D2 and α2-adrenergic receptors (to prevent auto-inhibition of DA and NE neurons, respectively) [12].

Old antidepressant drugs, such as tricyclic antidepressants or monoamine oxidase-A (MAO) inhibitors, are used in some treatment-resistant cases. These drugs are otherwise rarely prescribed because of their toxicity and strong side effects. The effectiveness of these drugs in SSRI-resistant depression may be explained, at least in part, by their ability to stimulate simultaneously 5-HT, NE, and DA transmission [12].

Non-pharmaceutical treatments of depression are psycho- and physiotherapy therapy, electroconvulsive therapy, transracial brain stimulation, deep brain stimulation, vagus nerve stimulation, sleep deprivation, and other strategies. Non-pharmaceutical treatments are used alone, or, more common, in combination with antidepressant drugs. The physiotherapeutic strategies in the treatment of depression and related mood and anxiety disorders have received attention only recently. The beneficial effect of physical exercise on the mood was known since antiquity: mens sana in corpore sano. Particularly, exercise has potent antidepressant and anxiolytic effect. It is possible that the modern life style, associated with decreased physical activity, contributes to the high prevalence of depression, anxiety and mood disorders. Regular, reasonable, and voluntary physical exercise has strong beneficial effects on the mood and emotional well-being. Exercise was reported to stimulate the general feeling of happiness [32] to improve sleep [16], memory and cognitive functions [23] to decrease stress and anxiety, and to contribute to the treatment of depression [9] bingo eating and obesity [42] as well as drug and alcohol abuse [20].

On the other hand, excessive exercise can be compulsive and addictive [7].

This compulsive form of exercise is often associated with eating disorders, such as anorexia and bulimia [43].

Although exercise has a crucial impact on the emotions and behavior, the neuronal mechanisms of this impact are almost completely unknown. Several studies, performed in the voluntary wheel running (VWR) rats, demonstrated of behavioral [33] and neurochemical [6, 36] alterations similar to the changes induced by antidepressant drugs. It was reported that certain behavioral effects of the VWR are similar to those induced by the selective serotonin (5-HT) inhibitor SSRI fluoxetine (duration of the swimming

during the voluntary swim test: FST), others to those persuaded by the selective norepinephrine (NE) reuptake inhibitor (SNaRIs) reboxetine and dual 5-HT/NE reuptake inhibitor (SNRI) venlafaxine (decrease in avoidance time during the elevated T-maze test: ETM) or benzodiazepine diazepam (increase in open arm time during the elevated P-maze: EPM) [33].

Monoamine systems of the brain (5-HT, NE, and dopamine: DA) are the primary targets of almost all known antidepressant drugs. Because of the similarity between the effects of VWR and some antidepressant drugs, it is possible that the effect of PE is mediated, at least in part, via monoamine pathways. However, other neuronal pathways might be involved as well. Because of their role in stress response and mood regulation, certain hypothalamic neuropeptides, such as β-endorphin, oxytocins, and vasopressin, are the principal candidates. The primary function of β-endorphin system is pain modulation. However, it has been reported that β-endorphin plays a fundamental role in reward, reinforcement, motivation, addiction, stress response and depression [26, 27]

It has been demonstrated that the deficiency of brain β-endorphin diminishes the effect of the VWR on adult hippocampal neurogenesis [31].

Oxytocin is known mainly as a hormone involved in the parturition and lactation. However, it has been described that oxytocin belongs to stress hormones and is increased in response to several stress stimuli in both the general circulation and in the brain [24, 25, 39].

Moreover, relation of oxytocin to depressive [15, 21, 38] and addictive-like [5, 35] behaviour has been described. Previous studies showed decreased oxytocin content in the posterior pituitary accompanied with a slight increase in hypothalamic oxytocin content as well as in oxytocin mRNA levels in the paraventricular nuclei in rats exposed to VWR [6, 35].

Similarly, vasopressin, hormone involved in the control of water-electrolyte balance, is released during stress and has been implicated in several mental processes [25].

The effect of VWR on vasopressin has not yet been directly examined, however, some anxiogenic and depressogenic effects of vasopressin have been reported [37].

Using in vivo electrophysiology, it was recently found that the VWR in ruts leads to the tonic activation of the 5-HT neurons in the dorsal raphe nucleus (DRN) [40].

Conclusions. Although the last-generation pharmaceutical compounds are used as a fist-line treatment for depression, non-pharmaceutical treatments are still used, either as a last-resort treatments when pharmaceutical strategies are insufficient (e.g., electroconvulsive therapy of invasive deep brain stimulations), or as adjuncts to antidepressant drugs to improve the outcome of the treatment (e.g., psychotherapy). Voluntary physical exercise can be an adjunct physiotherapeutic treatment in depression, given together with the pharmacotherapy, e.g., with SSRIs. One of the potential mechanisms of action of physical exercise in depression is stimulation of basic and/or reversal of the SSRI-induced inhibition of 5-HT tone. Other potential mechanisms, such as neuropeptide pathways, should be investigated in the future studies.

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Received 12 October 2016

УДК 378.172 DOI: 10.14529/hsm160409

НЕЙРОННЫЕ МЕХАНИЗМЫ ПОЛОЖИТЕЛЬНОГО ВЛИЯНИЯ ФИЗИЧЕСКИХ НАГРУЗОК НА НАСТРОЕНИЕ

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Цель: обобщение экспериментальных данных (полученных автором и его коллегами из других лабораторий) о нейронных механизмах воздействия физических нагрузок на настроение и интерпретация возможного механизма, лежащего в основе физической активности и стабилизирующего настроение. **Материалы и методы.** Соматическая депрессия – это нарушение мозговой деятельности, характеризующееся тяжелой эмоциональной, когнитивной, нейроэндокринной и соматической дисфункцией. Исходя из этой концепции, проведен анализ экспериментальных данных о различных способах ведения пациента с депрессией, включая медикаментозное лечение и воздействие физическими нагрузками. **Результаты.** Невзирая на то, что антидепрессанты последнего поколения имеют более высокую клиническую эффективность и надежность, их эффект начинает проявляться только спустя существенное время после начала курса лечения; кроме того, у значительного количества пациентов отмечается неадекватная реакция на действие таких препаратов и/или рецидив болезни, даже если лечение поначалу было успешным. Ряд немедикаментозных стратегий используется в качестве вспомогательных или замещающих средств, если терапия антидепрессантами оказывается неэффективной. К числу таких стратегий относится добровольная физическая нагрузка. **Выводы.** Добровольная физическая нагрузка может применяться как вспомогательный физиотерапевтический метод лечения депрессии, если используется вместе с фармакотерапией, включающей, например, селективные ингибиторы обратного захвата серотонина (SSRI). Один из возможных механизмов действия физической нагрузки при депрессии – стимуляция или изменение подавления серотонинергических рецепторов под влиянием SSRI. Другие возможные механизмы, в частности, нейропептидная регуляция, должны быть изучены более подробно в дальнейших исследованиях.

Ключевые слова: *депрессия, антидепрессанты, добровольная физическая нагрузка, серотонин, норадреналин, дофамин, нейропептиды, β-эндорфин, окситоцин, вазопрессин.*

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Поступила в редакцию 12 октября 2016 г.

ОБРАЗЕЦ ЦИТИРОВАНИЯ

Dremencov, E. Neuronal Mechanisms of the Beneficial Mood Effects of Physical Excercise / E. Dremencov // Человек. Спорт. Медицина. – 2016. – Т. 16, № 4. – С. 87–92. DOI: 10.14529/hsm160409

FOR CITATION

Dremencov E. Neuronal Mechanisms of the Beneficial Mood Effects of Physical Excercise. *Human. Sport. Medicine*, 2016, vol. 16, no. 4, pp. 87–92. DOI: 10.14529/hsm160409