An overview of hypotheses of antidepressant effects of exercise, Part 1: Biological mechanisms

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Abstract

The effect of exercise on depression has long been of interest. Many studies have demonstrated antidepressant effect of exercise intervention. They support the belief that exercise has been proven effective in improving depression.

By reviewing the relevant published articles, the purpose of this paper is to discuss the possible causality for the effects of exercise on depression. The mechanisms mediating the beneficial effects of exercise on mental health are unknown, although several hypotheses have been put forward. There are many possible explanations to how exercise works to alleviate depression, with some research done on each possible theory. The hypotheses stated so far by scientists are either biological or psychological. In biological classification, biochemical hypotheses are the regulation of chemicals such as hormones in the body or those associated with changes in the nervous system. On the other side, psychological theories cover the possibility of mental differences caused by exercise. In this review article, as part one, the reader are provided with the possible explanation of biological aspects which have been suggested through the literature on antidepressant effects of physical activities and exercise. Among biological assortment which including the physiological and biochemical hypotheses, the put forward hypotheses of catecholamine, endorphin, brain blood flow, Hypothalamus- Pituitary- Adrenal Axis model (HPA), monoamine, and thermogenic/ Pyrogen hypotheses have been discussed. A model that postulates the interplay of biological, psychological, and social factors will be required to explain adequately the mechanisms underlying the effects of physical activity on mental health. Whatever, the reason for the mood enhancing effects of exercise is not necessarily the most important point. The point is that engaging in physical activity has very powerful anti-depressive effects. There may be a combination of these hypotheses that can better explain the causality of the antidepressant effect of exercise.

Key words: Exercise, Depression, Hypothesis, Mechanism

Introduction

There is a strong correlation between participation in physical activity and anti-depressive effects and ample evidence regarding the strong association between exercise participation and reduction in depression has led researchers to propose several biological, physiological, social, cognitive and psychological mechanisms underlying this relationship. Accordingly, under the spotlight of experimental research findings, in attempt to explain results that have earlier been reported, many hypotheses have been developed for the aetiology of antidepressant exercise.

If a causal relationship exists between physical activity and depression, then experimental manipulation of physical activity should prevent or reduce depression. Although several hypotheses have been put forward, the mechanisms mediating the beneficial effects of exercise on mental health are unknown and research to date has not extensively examined the plausible mechanisms suggested in the literature. Mausner, & Kramer, (1985) [1] have suggested criteria widely used in epidemiology to evaluate the likelihood that an association is causal which included the following: strength of association, dose-response relationship, independence, consistency of association, temporal sequence, biological plausibility, and experimental confirmation. In order to determine whether there is a causal relationship between physical activity and depression, these relevant epidemiologic criteria must be explained in research investigating physical activity and depression associations.

A better understanding of the mechanisms behind the antidepressant effects of exercise would not only provide additional insight into a possible causal association, but should also be helpful in the future use of exercise as an adjunct therapy in the treatment of

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depression. Accordingly, there are many possible explanations to how exercise works to alleviate depression, with some research done on each possible theory. Under the spotlight of experimental research findings, however, researchers have attempted to put forward some explanations for the aetiology of anti-depressant effects of exercise. While none of the studies provides conclusive information on the question of mechanisms underlying these exercise-induced changes, there are a number of hypotheses that might help explain the positive effects of exercise on depression. A model that postulates the interplay of biological, psychological, and social factors will be required to explain adequately the mechanisms underlying the effects of physical activity on mental health. Several mechanisms from a variety of biological and psychosocial pathways have been hypothesized to mediate the antidepressant effects of exercise, but few have been supported by randomized, controlled trials.

Among biological assortment which including the physiological and biochemical hypotheses some are put forwarded as following: the catecholamine hypothesis, the endorphin hypothesis [2], brain blood flow hypothesis, Hypothalamus- Pituitary-Adrenal Axis model (HPA) [3], monoamine [4], and the hypotheses of thermogenic/ Pyrogen [5]. Biochemical hypotheses are the regulation of chemicals such as hormones in the body associated with changes in the nervous system and the biological basis of depression is centered in dysregulation of nervous system.

On the other side, psychological theories cover the possibility of mental differences caused by exercise. Possible psycho-social explanations such as subjective expectations, social interaction, attention, feelings of control, enhancement of social support [6], the mastery hypothesis, distraction from worries or time-out hypothesis (diversion from stressful stimuli) [6, 7], improved self-image [8, 9], and improvements in self-esteem[10] have also been posited to mediate the effects of physical activity on depression. However, design limitations such as inappropriate comparison groups and confounds between the exercise stimulus and psycho-social variables often preclude examination of such mechanisms. Although, these explanations remain plausible some of them have not been empirically tested in well-designed studies [11] and the exact mechanism explaining the exercise and depression relationship has not been yet clearly established. [12]. Different mechanisms may work for different people, and biological, psychological, and social mechanisms may work in concert with one another in an interactive manner [13]. Thus, it is reasonable to consider a combination of these hypotheses may

better explain the causality of the antidepressant effect of exercise. A model that postulates the interplay of biological, psychological, and social factors is required to explain adequately the mechanisms underlying the effects of physical activity on mental health.

Physiological hypotheses:

Physiological theories are associated with changes in the nervous system. Physiological hypotheses are established on the principle by which measurable increases on the level of physical fitness are as a prerequisite for psychological changes. In particular, for patients who have a decreased level of physical condition it has been considered important to normalize their physical work capacity. According to Simons el. al (1985) [14] the physiological explanation is based on the fact that exercise of sufficient duration, frequency, and intensity produces specific physiological changes. For example, decreased cardiovascular response to physical stress may be correlated with decreased response to emotional and psychological stress, which in turn might mitigate depressive reactions in response to such stress.

Cardiovascular Fitness hypothesis

If increasing levels of physical activity are associated with decreasing levels of depression, then it would provide evidence of a causal relationship. Accordingly, a reduction of cardiovascular response to physical tension may accompany with lessening response to psychological and emotional stress which in turn caused depressive responses to be declined to such a stress. This hypothesis is partly confirmed by findings implying the correlation between the level of physical fitness and mood status [14, 15]. However, several studies have mentioned that antidepressant effect of exercise happened within the first few weeks of treatment, prior to increasing in physical fitness level of subjects [16, 17, 18]. As a result, for the psychological gains, the important point seems to be the participation in exercise itself, not the acquisition of a fitness effect.

Thermogenic / Pyrogen hypothesis

The thermogenic model suggests that body temperature elevations cause reduce tonic muscle activity, in turn reducing somatic anxiety and mood improvements and positive psychological effects after exercise [19, 20, 21, 22]. During physical activity, the deep body temperate is elevated. It has been postulated that this transient warming may explain the psychological effects of exercise [23] and a rise

in core body temperature following exercise is responsible for the reduction in symptoms of depression. Hence exercise may act as a thermogenic stimulus to enhance mood. DeVries (1981)[20] explains that increases in temperature of specific brain regions, such as the brain stem, can lead to an overall feeling of relaxation and reduction in muscular tension. While this idea of increased body temperature has been proposed as a mechanism for the relationship between exercise and depression, the research conducted on the thermogenic hypothesis has examined the effect of exercise only on feelings of anxiety rather than depression [24]. In some literature this hypothesis has been alluded to as Pyrogen hypothesis. Pyrogen is substance which raises body temperature. Morgan has proposed this as one possible mechanism mediating the psychological effects of exercise [25]. Martinsen (1987) write that there is some animal research indicating that whole-body warming increases mood [26]. There are some indications that during affective illness there may be local disturbances in brain oxygenation and metabolism. Some have claimed that aerobic exercise is associated with an increase in brain oxygenation, but empirical evidence supporting this is not strong [26]. According to the evidences on relationship between physical fitness and depression it is mentioned that no causal link is demonstrated. Therefore physiological explanations are questionable yet. Developing the new, non offensive methods for dynamic measurements from circulation and cerebral metabolism may create an important prospect in the future research. Thus, for the moment, it seems reasonable to conclude that the temperature hypothesis still remains tenable [25].

Biochemical hypotheses:

Biochemical theories are the regulation of chemicals such as hormones in the body. Because, of difficulties and invasive procedures [26] in testing biochemical hypotheses in humans, advances in this research area are somewhat low. However, the biochemical and neurotransmitter systems depict a credible resources by which exercise could mediate depression. There are no studies examining the biological mechanisms that could explain the antidepressant effects of physical activity and exercise among humans, although, several research using animal models of stress and depression have been done in exercise psychology [27]. As the biological basis of depression is centered in dysregulation of monoamine system and the HPA axis [27], therefore it is considered three types of biochemical components to be related to this hypothesis: Brain Blood Flow, monoamines and beta endorphins.

Brain Blood Flow Hypothesis:

Brain blood flow is responsible for consistent nourishment to every brain cell, while sending extra flow to activate motor regions of the central nervous system on demand. Enhanced blood flow to brain regions involved in the regulation of emotion could mediate changes in mood with exercise. Neuroimaging studies of depressed patients have shown several abnormalities of regional cerebral blood flow [28]. Because of the close coupling of brain metabolism and cerebral blood flow (CBF), the question of a global or regional reduction of CBF in depression has been suggested as a possible correlate of the depressed mood and reduction of behavioural activities characteristic of the disorder [29]. Increased brain flow hypothesis has been suggested as an explanation for changes in mood during exercise. Animal research and human studies has demonstrated that blood flow to areas of the brain involved in movement increases during exercise. Because an increase in blood flow is associated with elevated cellular metabolism, enhanced blood flow to brain regions involved in the regulation of emotion could mediate changes in mood with exercise. However, it is not clear what changes occur in brain blood flow during exercise in human. Changes in regional distribution consistent with altered mechanism in brain areas most associated with emotions, such as the frontal cortex or limbic areas, have not been shown [27]. Brain imaging has not been used to the study of depression after exercise. Because alterations in blood flow to brain areas that function in emotion have not been reliably shown during exercise, there is currently little evidence to support the role of brain blood flow in mediating the effect of exercise on depression [11].

Monoamine hypothesis:

Monoamines are a class of neurotransmitters in the brain that includes dopamine, norepinephrine (NE) and serotonin (5-HT). The monoamine hypothesis is based on the association between levels of NE and/or serotonin and depression. There is some evidence from a biochemical aspect that the amino metabolites secretion decrease in depressed patients. It is believed that depression is the result of a dysregulation in the biogenic monoamine system. Monoamine hypothesis for depression is suggested since detecting antidepressant effect of reserpine. This medication is a compound of the alkaloid class obtained from a snakeroot plant, used in the treatment of hypertension. It controls blood pressure by inactivating storage granules containing NE and 5-HT in peripheral nerves, thus decreases the activity of monoaminergic neurons. As researchers have

found that the symptoms of depression do not respond to drugs acting on dopamine, thus research has now focused on NE and 5-HT [30].

Physical treatments such as medication (Tricyclic antidepressant (TCA), Monoamine Oxides Inhibitors) and Electro-convulsive Therapy (ECT) that are effective on depression may accelerate the transfer of synoptic aminergic. Many researches on depression have focused on the brain monoaminergic systems, specially noradrenergic and serotonergic systems. Alterations in monoaminergic activity have been implicated in the pathogenesis and treatment of depression [31, 32, 33], with various studies examining the contributions of serotonergic [34, 35, 36] and noradrenergic systems [37, 38, 39]. Moreover, it is proposed that serotonin depletion caused depression by permitting the fall in NE levels. Serotonin depletion is unlikely a sufficient explanation for the occurrence of depression [40]. Doyn, et.al (1987) [41] expressed that at a biochemical level, the antidepressant may be explained with an increased aminergic transmission and short-term elevations in norepinephrine (NE) [41].

Accordingly, the monoamine hypothesis has been proposed as another mechanism to explain the depression-reducing effect of exercise. Mood improvement gained from exercises probably is due to aminergic transmission enhancement [14]. Exercise leads to an increase in the availability of brain neurotransmitters that are diminished with depression. They are also altered through exercise (e.g., increased release, increased uptake, etc.). These neurotransmitters increase in plasma and urine following exercise, but whether exercise leads to an increase in neurotransmitters in the brain remains unknown. Animal studies suggest that exercise increases serotonin and norepinephrine in various brain regions [42, 4, 43, 44]. But, to date, this relationship has not been studied in humans, [24] largely because it is rather difficult to assess levels of these neurotransmitters in intact humans [45]. Moreover procedures used to directly study the monoaminergic systems are extremely invasive.

Therefore, the limitations of the biogenic amine theory in explaining the pathophysiology of depression [40] and difficulties to prove the role of physical activity in regulation of brain neurotransmitters, and inconsistency of empirical evidence have led researchers to continue the search for new etiologic models of antidepressant effect of exercise.

Endorphin hypothesis:

The endogenous opioid peptides which so-called "heroin within" are endowed with the power to relive pain [46], cause generalized analgesia [47,48] and allow one to experience "runner's high" [49,

50, 51, 52,53]. Endogenous opioid systems play a critical role in modulating a large number of sensory, motivational, emotional, and cognitive functions [54].

β-endorphins are endogenous proopiomelano-cortin- derived opioids released primarily from the adenohypophysis [54**Error! Bookmark not defined.**]. Their release is believed to be triggered by stress. They are part of the mood regulating chemicals [55] that reduces pain and can even induce euphoria [56, 7] lead to an overall enhanced sense of well-being [24**Error! Bookmark not defined.**].

It has been found that people suffering with mood disorders such as depression have lower levels of these hormones and clinical depression has been associated with alterations in release of β-endorphin [57, 58, 59,60] Furthermore, some research has described the elevated circulating levels of β-endorphin in depressed patients [61] while some have not find [62].

An increase in the blood level of endorphins during vigorous physical exercise and heightened levels of endorphins may produce a state of euphoria and elevated mood. The endorphin hypothesis predicts that physical activity has a positive effect on psychological well-being, improved mood [63] and mental health [2, 4, 7, 64, 65, 66]. In particular, 'euphoria' and depression is caused by an increased release of endogenous opioids such as β-endorphins to receptor sites in the brain following exercise [24]. It is possible that the antidepressant effects of exercise are mediated, in part, by β-endorphins. Exercise may partially relieve depression, perhaps by generating endorphins [67, 30].

In animals, the repeated activation of endogenous opioid systems by exercise leads to tolerance and withdrawal phenomena [68, 69, 70].

Endorphin has been shown to cause an elevation and exercise elevates plasma endorphins. Data in man also indicate that endorphin systems are activated during long-lasting physical exercise, i.e. jogging, since the plasma β-endorphin level is elevated after running in many joggers [71, 72, 73]. However, the elevations in fit individuals are lower than in those who are not fit [74]. Moreover, untrained individuals, who performed a submaximal exercise bout, have similarly shown elevated plasma B-endorphin levels [75]. Besides, it has been shown that the concentration of ß-endorphin in the blood plasma compared to other substances, even after physical activity, was very low [76].

To date, the elevation of endorphins during exercise has been noted only in blood plasma rather than in cerebrospinal fluid [77]. The debate remains concerning whether peripheral endorphins reflect endorphin activity in the brain [78]. Because of the

inherent problems of examining β-endorphin receptor site occupancy in humans, research has attempted to examine peripheral β-endorphin levels after exercise [79, 80]. Although some research in human studies have shown a connection between peripheral beta-endorphin level and chronic pain [81,82] analgesic activity during stressful events [83,84] and while opioid-mediated analgesia could indirectly influence mood[66], exercise-induced analgesia has not yet been shown to explain subsequently improved mood in humans [7, 85, 86]. As endorphins are unable to cross the blood-brain barrier, it is unlikely that blood plasma endorphin levels can have a direct effect on people's mood state. Therefore, it is considered as a principal problem [87] that plagued the endorphin hypothesis.

Because of limitation in human data and being impractically of obtaining central nervous system (CNS) samples, measuring of endorphin levels in the human CNS is a highly invasive procedure that would in itself cause affective and biological changes [86, 88]. Also, ethical reason is considered as a limiting factor precluding the determination of central concentrations of endorphins. Interestingly, despite very limited support, the endorphin hypothesis remains one of the most popular explanations of the psychological benefits of exercise [80].

HPA Hypothesis:

The hypothalamic-pituitary-adrenal axis (HPA) - an intricate system- consists of a series of hormones which, under normal circumstances, are kept in homeostatic balance by multiple feedback regulatory mechanisms [89, 90]. Such a neuroendocrine system is designed to allow organisms to adapt to physical and psychosocial changes in their environments and closely associated with stress in mammals [91]. It together with the arousal and autonomic nervous systems, constitutes the stress system [92, 93, 94]. The HPA axis controls the secretion of corticotrophin-releasing hormone (CRH), Adrenocorticotrophic hormone (ACTH), and sensitive regulation of cortisol [95, 96,97]. ACTH is a peptide which its secretion intrinsically from the anterior pituitary is under the control of CRH [98]. ACTH control release of cortisol and cortisol is assumed to have an important role in adaptive reactions. The integrated function of this system is to proper the body for fight of flight in response to a real or perceived threat [11**Error! Bookmark not defined.**].

Excess activation and disruption of the HPA axis has also been involved in the aetiology of depression. Having substantial literature documentation of link between MDD and HPA activity, altered HPA functioning is one possible mechanism linking stress and the aetiology of depression [99, 100, 101, 102, 103, 104, 105]. With respect to the pathophysiology of depression it is hypothesized that the increased activity of a stress-sensitive HPA axis and noradrenergic neurons manifest depressive symptoms [106,107]. Chronic stress often precedes the onset of clinical depression [108] and a strong stressor increases the likelihood of manifestation of depression [109]. Symptoms of depression, such as weight loss [110,111] and sleep disturbances [112] have been attributed to dysregulation of the HPA axis [27, 113]. An overall increase in ACTH, a loss of sensitivity in steroid-negative feedback [27, 114, 71, 102, 115] and an increased activity of CRH pathways have been observed with depression [116, 117,118]. Moreover, antidepressants have been shown to normalize this excessive activation of the HPA axis in patients with major depression [119].

While, depression is usually marked by an hyperactivity of the HPA axis, and exercise training may lead to an attenuation of the HPA axis response to stress during standard exercise [120] , effects of exercise on the regulation of the HPA axis response to stress may be another medium by which exercise affects depression[27**Error! Bookmark not defined.**, 119]. Trained individuals exhibit an attenuated HPA axis response to exercise challenge and mental stress [119, 121, 122] this suggests that exercise may reduce depression, in part, by regulating the HPA axis response to stress.

Some limitations have been considered on research of HPA activity in depressed patients. For example, the effect of depression on HPA responses to stress may differ by the time of day or the basal, stress onset or recovery phases of HPA examination and even between individuals, and situations [119]. Moreover, dysregulation of HPA is variable among depressed people. Besides, the shift from the activation of the HPA-axis following stress to the distinct dysregulations of the axis associated with psychological and physical disturbances remains unexplained, so that firm conclusions concerning the aetiology and treatment of stress-related bodily disorders must be studied further [118]. And finally, no determined relation between basal HPA function [123,124;125] or response to the dexamethasone suppression test [126] and depression has been established yet [127]. Although exercise-induced adaptation of the HPA axis may ease the regulation of biological elements causing depression, however the effect of exercise training on this system in relation to depression is unclear [11]. There are practically no studies examining the biological mechanisms that could explain the antidepressant effects of physical activity and exercise among humans and future research is needed to

evaluate the effectiveness of exercise training on the HPA axis and to determine how these effects may influence depression [27].

Conclusion:

Notwithstanding the fact that the mechanisms responsible for exercise-related improvements in depression are not known, a number of potential mechanisms have been stated and discussed briefly to highlight the possibilities of how exercise exerts its influence of alleviating depression and associated symptoms. Although these mechanisms are plausible, a direct causal relationship between physical activity and depression has not yet extensively and empirically tested. research to date is not definitive, studies supporting psycho- physiological explanations has been weak, with some studies being poorly designed. No consensus exists regarding the relative importance of the above mentioned psychological and physiological hypotheses in explaining the association between physical activity and mood improvement. Given the level of knowledge and amount of research carried out on this subject, reliance upon a single mechanism to explain the relationship may be too simplistic. Additionally, different mechanisms may be important at specific times in the natural course of depression. It is highly likely that the influence of exercise on depressive symptoms exerts its effect by a number, if not all of the possible mechanisms in a combined manner or in a series of biological, psychological, and sociological factors. Such mechanisms are promising targets for future research in the area of exercise and depression. In future research using a combining psychobiological model must be clarified the plausible mechanisms that might explain the previously documented association between exercise and reduced depression. In such model, psychological and biological factors will interact in a specific and concatenate manner and the gender and individual differences should be considered in reaction with environmental impetus.

The proposed psycho-social mechanism cited for the antidepressant effect of physical activity and exercise will be discussed as part two in a next paper.

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