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Can Exercise Make Us Smarter, Happier, and Have More Neurons? A Hormetic Perspective

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ABSTRACT

The level of intensity in a fitness regimen determines its impact: exercising can enhance intelligence, boost happiness, and increase the number of neurons. It is commonly accepted that exercise programs yield both positive and negative outcomes, depending on their intensity, among other factors, following a pattern like hormesis with a two-phase dose response. In simple terms, hormetic stress is the exact amount of stress to which our body is challenged, but we are not too tired. Therefore, your body is not weakened by lack of exposure to stress, but you are spared from the harmful side effects of toxic stress. Nevertheless, no proof has emerged thus far regarding a two-phase reaction of specific agents responsible for these exercise-induced effects. The discussions and concepts will revolve around adult hippocampal neurogenesis (AHN) as a plausible physiological basis for the hermetic reaction to exercise in relation to its impact on cognition and mood, including the potential molecular pathways that might facilitate these effects.

INTRODUCTION

Dishman et al. (2006) discovered that physical activity had wide-ranging effects on the entire body, including the brain. The positive impacts of physical exercise on cognition and mood can be elucidated through hormetic (biphasic) dose-response patterns, as Mattson (2012) suggested. Many of these effects are intricately connected to Adult Hippocampal Neurogenesis (AHN) in adults, a discovery made over the past decade (*Kempermann*, 2011), which refers to the generation of new neurons in adults, mainly influenced by exercise. These newly formed neurons are notably responsive to physical activity. Additionally, AHN has been associated with various behaviours and moods related to the hippocampus, irrespective of their association with exercise (*Kempermann*, 2011).

Using this knowledge, we first assessed the literature on the impacts of exercise's hormetic profile and the molecular agents affecting the brain. Based on this information, the authors proposed and investigated whether the reaction of AHN to exercise demonstrates a biphasic/hormetic dosage response and whether specific potential mechanisms supporting this reaction pattern might be identified in existing literature.

The response to this statement is critical not only for our understanding of exercise neurobiology but also for improving AHN (hormesis), which can readily affect and increase our efforts to modify adult neurogenesis outside of exercise (drugs or other therapies).

Exercise has long been acknowledged to have a favourable impact on a person's brain and well-being. Exercise not only increases intelligence but also increases happiness and even the number of neurons

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in the brain. However, it is crucial to note that the impacts of exercise are not consistent for everyone; instead, they vary based on the dosage of the exercise regimen. The concept of hormetic stress, that is, when the body is exposed to sufficient stress to stimulate an adaptive response without damaging it, becomes relevant in this context. Therefore, it is essential to understand the biphasic dose response to exercise, where appropriate exercise intensity produces benefits, while exercise that is too vigorous can have adverse effects. However, to date, there is insufficient evidence regarding the potential mediators involved in this biphasic dose response.

Recent research in this area has highlighted the importance of exercise intensity in influencing the exercise response to cognition and mood. Recent research has also identified variables that influence AHN as a potential physiological foundation for the hormetic reaction to exercise. However, a limitation of recent studies is that they have yet to reveal the molecular mechanisms that may mediate these effects fully.

Although there have been several studies leading to an understanding of the relationship between exercise intensity, adult hippocampal neurogenesis, and hormetic effects, there still needs to be a gap in understanding the molecular mechanisms that link these. Some studies also noted differences between their findings and those of other studies, which require further clarification. Therefore, we need to explore further how exercise influences neurogenesis and mood through a comprehensive and integrated approach.

Based on the identified gap analysis, this study aimed to provide more clarity on the biphasic dose response concerning exercise, explicitly concentrating on adult hippocampal neurogenesis (AHN) as a potential intermediary. The authors will seek a deeper understanding of the molecular mechanisms that play a role in linking exercise, neurogenesis, cognition, and mood. The study will also seek to differentiate the impacts of varying exercise intensities on the body and brain. Thus, this research will make a new contribution to the understanding of the link between exercise, neurogenesis, and mental well-being.

METHODS

The method of conducting a literature review is a systematic process that involves defining the research objectives, establishing a search strategy, selecting relevant sources, critically evaluating their quality, categorising and grouping them based on emerging themes, and finally, synthesizing the main findings to provide a comprehensive understanding of the research area. A literature review helps researchers build a strong foundation for their investigations, identifies gaps in the existing knowledge, and contributes to the broader academic discourse.

RESULTS

Exercise and the Brain

Furthermore, the connection between physical exercise and cognitive function in the brain is not a mere coincidence; instead, it closely aligns with the individual's level of physical activity (Foster, 2015). What is noteworthy is that physical activity triggers both structural and functional changes in the brain. This adaptive plasticity in the brain enables it to adapt its neuronal resources to meet the varying demands of information processing (Chen & Tonegawa, 1997). These changes encompass aspects such as neuronal cell metabolism, gene expression, cell size, dendritic structure, synaptic count, blood-brain barrier properties, and synaptic plasticity. Beyond these alterations to existing cells, neural resources also encompass a concept known as meta plasticity, particularly adult neurogenesis, which involves recruiting additional neurons through cellular and synaptic modifications in specific regions of the adult brain (García-Capdevila et al., 2009).

In this context, it is unsurprising that physical exercise regimens have frequently been documented to actively enhance synaptic plasticity, nerve cell metabolism, and blood circulation in specific brain regions.

This improvement in neural processing abilities has been observed in various human populations, including adults, children, and teenagers. Furthermore, when compared to other primates, humans have a distinctive talent for endurance running (Mattson, 2012). Regular exercise improves numerous parameters related to neurodegenerative illnesses and produces neuroprotection in all investigated brain areas. Finally, exercise has been reported to be an effective technique for reversing the symptoms of some neurodegenerative diseases as well as numerous brain impairments and disorders (Dishman et al., 2006; Mattson, 2012).

From a mechanistic viewpoint, physical activity can enhance blood circulation (Lucas et al., 2015) and modulate growth factor signalling pathways, particularly insulin-like growth factor 1 (IGF-1), which functions as a hormone that governs the impacts of growth hormone (GH) in the body, promoting the average growth of bones and tissues (Llorens-Martín et al., 2008). Additionally, exercise influences brain-derived neurotrophic factor (BDNF), as highlighted by Gomez-Pinilla and Hillman in (2013). Moreover, it impacts the Vascular Endothelial Growth Factor (VEGF), a protein pivotal in the process of angiogenesis.

Angiogenesis refers to the creation of fresh blood vessels. According to Meng (2006) VEGF is a protein that improves the availability and activity of neurotransmitters (particularly dopamine, glutamate, norepinephrine, and serotonin). Sport, on the other hand, has negative consequences that cannot be separated. These stressors include thermal, metabolic, hypoxic, and oxidative stress, as well as mechanical stress (Peake et al., 2015).

Humans exhibit increased running endurance, representing one aspect of the hormetic response. This response involves a low-dose stressor that triggers an adaptive reaction, improving the ability to endure and cope with moderate to intense levels of stress (Calabrese et al., 2007; Mattson, 2012). Nonetheless, multiple research endeavours have shown an inverted U performance curve in cognitive function following exercise in humans (Tomporowski, 2003). This correlation is complex and significantly affected by the duration of the intense but short-lived effort, which often results in a swift restoration of an individual's abilities alongside the individual's initial fitness level before the research. This factor contributes to the absence of a clear-cut impact concerning brief, intense workout routines (Tomporowski, 2003). Additionally, motivation to engage in acute exercise or long-term resistance training significantly influences any conclusions drawn about the association between exercise and cognitive performance in humans.

Continuous aerobic activity, however, results in reduced information processing and cognitive function, which is contingent upon the level of dehydration, a factor varying with the workout duration. As anticipated, exercise leads to increased oxidative stress due to heightened oxygen utilisation by the body during physical activity, which is closely linked to fluctuations in the way energy is metabolised. This aspect of an exercise regimen significantly contributes to the adverse impacts of intense workouts.

While it is widely acknowledged that exercise produces non-linear response patterns, including hormetic effects, across various studied outcomes (Radak et al., 2008), it is essential to understand that this biphasic reaction is closely linked to oxidative stress, oxygen consumption, and mitochondrial metabolism. All available evidence underscores its influence on the entire body, especially on muscles and the cardiovascular system. Regarding the brain, it is essential to note that exercise enhances the production of reactive oxygen species (ROS), antioxidant enzymes, and redox signalling within the body. Circulating factors also have the potential to induce oxidative stress (Calabrese et al., 2007). Since the generally positive effects of exercise on brain oxidative stress are primarily attributed to the increased activity of antioxidant enzymes as summarised by Radak et al., (2008), it is recommended that there be a sophisticated regulation and balance between the induction of exercise-related systemic stress.

ROS can modify unsaturated fats through oxidation, influencing the brain's flexibility and physical condition. Brain antioxidant enzymes participate in the brain's reaction to exercise following a bell-shaped

hormesis curve. High ROS levels can induce oxidative harm, while moderate ROS levels might stimulate adaptive reactions (Radak et al., 2008).

Biphasic Responses to Exercise Cognition and Mood

This study did not try to discover which specific qualities are ideal for obtaining favorable or adverse effects with exercise training protocols, as comparisons between different activities have been found in several meta-analyses to be highly challenging due to the difficulty of comparing training intensity degrees between research, and since more is needed about the numerous training regime characteristics that influence training results. What is most important in this study is whether the authors discovered a biphasic response regardless of the methodology used. The cognitive approach is the framework in psychology which focuses on understanding how humans process information, organize knowledge, and apply it in problem-solving and decision-making.

To the best of the authors' knowledge, very few research have found that high-intensity exercise improves cognition. One study that stands out is one that found increased memory performance in a heavy exercise program and overtraining in a passive avoidance test (Ogonovszky et al., 2005). Surprisingly, the study found increased BDNF (Brain-derived neurotrophic factor) levels. It is a neurotrophin factor that influences supporting the formation and development of neurons and maintaining the existence of neurons only in the group that did the most intense exercise.

The response of hormesis to exercise has biological significance. A sedentary lifestyle has a negative impact on brain function, whereas exercise is one of the critical behaviors that help maintain health. It is rational to anticipate that the benefits of exercise become more favourable as one transitions from inactive tasks to exercise of moderate and high intensity. The exercise response is expected to display a sigmoidal pattern, constrained by certain thresholds: past a certain point of exercise intensity, duration, or frequency, there will not be further accumulation of positive effects due to the inherent limits of the body and brain's exercise capacity. Alterations in reaction to physical activity and maximal capacity to modify body and brain performance do not always increase linearly. The evidence that has been highlighted suggests this. The response to exercise typically aligns more with hormesis profiles, where increments in intensity, duration, or frequency of training can lead to the loss of the favourable effects experienced with low to moderate-intensity exercise. Why does this occur? As mentioned earlier, exercise serves as a form of stress. The beneficial effects of exercise on different body systems like muscles, bones, the immune system, the cardiovascular system, and the brain improve overall health and increase the body's ability to manage additional stress. However, there is a specific level of intensity where exercise-induced stress can result in less favourable outcomes, and sometimes, it might even cause adverse effects (exhibiting inverted U-shaped or even inverted J-shaped hormesis curves). This is due to the prolonged influence of hormonal stress throughout the entire body. Thus, the natural stress linked to physical activity is believed to significantly impact the hormesis pattern observed in the response to exercise. However, the following will present an explanation of the second biological evolutionary advantage of the hormetic response to exercise, focusing on AHN.

Molecular Mediators of Exercise Action

Exercise exerts both beneficial and detrimental influences on the brain. Among the critical factors at play is the array of growth factors stimulated by physical activity, including IGF1, BDNF, and VEGF (Dishman et al., 2006; Llorens-Martín et al., 2008), which are believed to underlie most of the positive effects, in addition to its anti-inflammatory actions (Silverman & Deuster, 2014). Conversely, oxidative stress signalling is recognised as the most significant adverse factor post-exercise. Another critical element influencing the outcomes of exercise training programs is the individual's dietary and lifestyle choices (Gomez-Pinilla & Hillman, 2013). However, this review's scope is insufficient for an exhaustive exploration of

the various molecular agents that govern the effects of exercise. A well-established consensus (Mattson, 2012) identifies physical and cognitive activity, along with control of nutrient intake, as triggers for mild metabolic stress in neuronal cells. This pathway activates multiple transcription factors, such as CREB and NF-kB, which, in turn, regulate the expression of BDNF and anti-apoptotic genes (such as Bcl-2). These factors promote cell survival, synaptic plasticity, and neurogenesis processes.

The objective of this study is to emphasize the growing body of evidence indicating that both the positive and negative effects of exercise are typically regulated by the same factors, following a biphasic dose-response pattern akin to hormesis. For example, many of the beneficial outcomes of exercise depend on the concurrent increase in BDNF (Mattson, 2012) and IGF1 (Llorens-Martín et al., 2008), in conjunction with the interplay between caloric restriction and an individual's activity level (Mattson, 2012) However, elevated levels of BDNF and IGF1 can be detrimental to the brain, and dietary intake is associated with the risk of neurodegenerative diseases following a biphasic dose-response curve. Furthermore, it is not surprising that all these factors and lifestyle choices are linked to energy balance.

While all the factors discussed above play a direct role in the effects of physical exercise on cognition and mood, recent research over the past decade has revealed a strong connection between adult neurogenesis and these changes, with adult neurogenesis being directly influenced by such growth factors.

Actions of Exercise and Adult Hippocampal Neurogenesis

Adult neurogenesis refers to the process of generating functional new neurons in the adult brain (*Kempermann*, 2011). It is widely recognised that exercise impacts the rate of mature neurogenesis and influences the creation of new nerve cells in both the hippocampus and olfactory system. Additionally, enriched environments are known to enhance the survival of immature nerve cells, as outlined in seminal reviews by Mattson (2012), Olson et al. (2006), and in a comprehensive recent review. While some data suggest that exercise may affect the olfactory system, there are conflicting reports as well (Bekinschtein et al., 2011). This experience-induced plasticity has been suggested as a necessary process for optimising brain function (Opendak & Gould, 2015). Several mechanisms have been strongly linked to the impact of exercise on AHN, the most notable of which include IGF1 (Llorens-Martín et al., 2008), BDNF (Bekinschtein et al., 2011; Chen & Tonegawa, 1997; Rothmann & Cooper, 2015).

The Biphasic Response of Adult Hippocampal Neurogenesis

AHN shows a response pattern like hormesis, displaying a non-linear curve after various treatments or interventions. At low concentrations, glucocorticoids (Glucocorticoid hormones are steroids that have 21 carbon atoms with the primary function of increasing gluconeogenesis) stimulate beneficial and protective responses in hippocampal dentate granule neurons through mineralocorticoid receptors. In contrast, at higher concentrations, deleterious effects are achieved via glucocorticoid receptors. A situation like this occurs when we talk about the impact of glucocorticoids on AHN (Leuner et al., 2012) When the glucocorticoid receptor (GR) is minimally activated, like in less stimulating environments or with a less active lifestyle, adult neurogenesis remains at low levels—both in cell production and maturation. However, in enriched environments, frequent moderate physical activity or acquiring knowledge, the GR gets activated to an average level, resulting in a baseline of AHN. On the flip side, high GR activity caused by uncontrolled stress significantly reduces neurogenesis by affecting the creation and development of immature brain cells. This situation creates a response pattern shaped like an upside-down U (Saaltink & Vreugdenhil, 2014). The mechanism that stops the cell growth caused by adrenal steroids in the dentate gyrus (Gould & Tanapat, 1999) is influenced by the N-Methyl-D-aspartate receptor.

Apart from the widely recognised instances of hormetic reactions, recent evidence has accumulated with more examples. For instance, when neural stem cells are exposed to mild doses of chemical, physical, or drug-induced stimuli (while high levels could be toxic), they protect these cell precursors in situations of

neurodegenerative diseases (Wang, 2014). A new study revealed that the positive effects of calorie restriction on generating new brain cells are controlled by the appetite-stimulating hormone receptor acyl-ghrelin and the gene activator Egr1 (Hornsby et al., 2016). This hormone receptor plays a role in the hormesis-like reaction of AHN to maintain a balance in energy levels. Similarly, specific components found in ginseng exhibit beneficial effects on forming new neurons but in a manner that depends on the dose and time, as shown by Liu et al. (2008). This characteristic is also found in many plant-based chemicals reviewed by Mattson et al. (2012). The range of reactions of adult neurogenesis to different substances is extensive, including oxytocin, bisphenol, allopregnanolone, exposure to lead poisoning, statin, and even fluoxetine. However, both VEGF and TGF-β exhibit dual effects on the process of neurogenesis. Higher doses of VEGF reduce the presence of natural VEGF receptors leading to more mature neurons but less production of new cells). Lower doses increase the number of VEGF receptors (without a noticeable effect on producing new cells or their maturity, Meng et al., (2006). Lower amounts of TGF-β promote the creation of new brain cells, while higher levels trigger programmed cell death in the growth of the autonomic nervous system.

As more evidence supports the biphasic reaction to exercise impacting diverse brain aspects like cognition and mood, along with the biphasic reaction of AHN to different factors, the AHN has been suggested as a pivotal mediator in multiple aspects. When examining the impacts of exercise, the subsequent query arises about whether there exists a biphasic response of the AHN to exercise.

First Hypothesis and Evidence Supporting a Biphasic Response of Adult Hippocampal Neurogenesis to Exercise

Based on indirect evidence and two recent direct findings, the authors propose the theory that AHN serves as a physiological basis for hormetic responses induced by physical activity, influencing cognition and mood. To verify this hypothesis, they propose examining various AHN-related parameters' responses to different levels of exercise intensity, particularly intensities higher than the lactate (anaerobic) threshold. They argue that this hypothesis aligns better with the mentioned literature, recent direct evidence, and prospective data testing this effect, as opposed to the currently established sigmoidal dose-response. However, it is acknowledged that the dose response of AHN to exercise is a well-established fact (Holmes et al., 2004). Initially, this answer is monotonous, as increases in training intensity (training volume) from a sedentary basal level rapidly led to an increase in the rate of neurogenesis. Only a little evidence has been gathered regarding a biphasic response when the intensity of the exercise reaches a gruelling or very high level. As far as the authors are aware, there are only a few findings have presented evidence in this direction. One research study noted heightened neurogenesis (observed through BrdU/NeuN labelling without employing stereological methods) and increased mRNA levels of BDNF, NMDAR1, and Flk-1, solely following low-intensity exercise. Conversely, high-intensity exercise resulted in the restoration of all parameters to baseline levels without exhibiting substantial alterations (Lou et al., 2008).

Notably, the benefits of neurogenesis induced by slightly stressful (mild) exercise are contingent upon the activation of glucocorticoid receptors, implying a supportive and permissive function of these receptors and moderate glucocorticoid levels during moderate exercise. This information, combined with the previously discussed hormetic-like reaction to hippocampal glucocorticoid action, suggests that glucocorticoid receptors are a highly likely mechanism mediating the hormetic and biphasic reaction of AHN to varying levels of workout intensity. However, the glucocorticoid receptor is not the sole factor at play in this process.

Ultimately, several studies found that different types of hormetic responses of AHNs to training exist despite the absence of pro-proliferative solid effects produced by training (Kronenberg et al., 2006). As a result, the hormetic reaction in adult neurogenesis due to training is observable not just from increasing doses but also over extended periods of training.

It is essential to be mindful of one's biological state towards exercise, as intrinsic stress associated with exercise beyond a certain threshold can trigger harmful stress hormones that eliminate the benefits of exercise on the body, including the brain. This sensitivity to hormones holds more relevance for the adult hippocampus, as higher brain regions regulate stress hormone levels in the body. Additionally, the specific sensitivity of the Adult Hippocampal Neurogenesis (AHN) to stress hormone concentrations should be considered. Moreover, the authors put forward an alternative explanation for this pattern, specifically in relation to adult-generated neurons. It is theorised that an elevated quantity of new neurons in the adult hippocampus might not necessarily be beneficial; instead, an excessively high number of new neurons could be detrimental to the functioning of the tri-synaptic hippocampal circuits. Excessive immature neurons exhibit distinct electrophysiological, morphological, and connectivity characteristics, and their incorporation into a fully mature circuit, which includes mature granule neurons with diverse physiological properties, could potentially disrupt system function, especially after intense exercise. The findings presented in this study are most accurately understood within the context of the proposed hypothesis, representing an adjustment to extremely high-intensity exercise, preventing the excessive accumulation of new neurons beyond a certain threshold, leading to a U-shaped response.

Mechanisms of the Biphasic Response of Adult Hippocampal Neurogenesis to Exercise

Based on the mentioned literature, as a second part of the Authors' hypothesis, they also suggest that growth factors (such as IGF1 and BDNF, which are significant key factors) that mediate the effect of exercise on AHN can control this response curve. Besides GR, various other mediators responsible for the influence of exercise on adult hippocampal neurogenesis (AHN) have been observed to exhibit dose-response patterns reminiscent of hormesis for different brain parameters, not limited to neurogenesis. These factors could play a role in mediating the biphasic response of neurogenesis. IGF1 is one such factor, with repeated exercise sessions either showing no change or even a decrease in serum levels, as reported by Kramer et al. in (1995), while long-term exercise raised IGF1 levels above their pre-exercise baseline, as shown by Eliakim et al. in (2006). IGF1 is known to safeguard neurons at lower concentrations, but at higher levels, it may have no effect or even produce a counteractive impact. This biphasic pattern has been observed in both live animal studies (Johnston et al., 1996) and controlled laboratory experiments. The precise mechanism behind the biphasic effects of IGF1 on the brain remains somewhat unclear. However, one plausible explanation is the well-documented biphasic effects of insulin-like growth hormone binding proteins, which regulate the availability of IGF at conventional IGF receptors. For example, in the choroid plexus, IGFBP2 enhances the biological effects of IGF1 at lower concentrations but diminishes its effects at higher concentrations, as demonstrated by Delhanty and Han (1993). This biphasic action of IGF1 has also been observed in other organs, such as the kidney (Wang, 2014) and muscle. Similarly, the secretion of VEGF in retinal epithelial cells, which regulates cell proliferation, displays a hormesis-like response to hydroxynonenal when exposed to oxidative stress. (Vatsyayan et al., 2012).

In the end, the influence of reactive oxygen species (ROS) may play a role in mediating hormesis in response to exercise (Radak et al., 2008). As previously mentioned, ROS are substances generated during exercise, the extent of which depends on their intensity. Oxidative stress represents a fundamental and crucial reaction to the "alterations in redox homeostasis" induced by exercise, as outlined by Nikolaidis et al. in (2012). Depending on their concentrations, ROS can serve as regulators in signalling processes, maintaining redox balance, or they can be harmful to essential cellular components. Low levels of ROS provoke a moderate stress response, while high levels can lead to excessive stress, especially during high-intensity exercise, exhibiting a typical U-shaped dose-response pattern. This hormetic profile reflects an adaptive response to stress, where mild to moderate challenges enhance the resilience of various organ systems against higher levels of stress. Although ROS produced through exercise can cause oxidative

damage to lipids, proteins, and DNA, they also activate redox-sensitive transcription factors and signalling pathways necessary for adaptive responses (Mattson, 2012; Radak et al., 2008).

Similarly, various other factors that exhibit biphasic dose-response curves, such as hormones, also have significant relevance. An example that illustrates this is the potential detrimental impact of forced exercise on a treadmill after deep brain surgery (Jun et al., 2012). These findings can be interpreted that surgery reduces the positive reaction to exercise and shortens the hormesis zone in a biphasic effect (Calabrese et al., 2007). In response to this, recent research has shown that exercise intensity must be reduced following previously experienced stress to effectively produce positive effects that are often assessed through a variety of physiological parameters (Kim et al., 2015)

CONCLUSION

Multiple studies have shown that adult neurogenesis (AHN) demonstrates effects characterised by a biphasic response akin to hormesis when subjected to exercise. Moreover, various research reports indicate that the molecular agents influencing the impact of exercise on neurogenesis also exhibit a biphasic pattern regardless of their direct involvement in the effects on AHN caused by exercise. Considering these sets of evidence, the Authors propose a hypothesis suggesting that adult neurogenesis serves as the foundational basis for the hormetic reactions regarding cognition and mood resulting from exercise. Additionally, growth factors like IGF1 and BDNF, recognised as pivotal elements in mediating the influence of exercise on AHN, are considered plausible candidates for mediating this response pattern in conjunction with ROS.

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