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Exercise-induced Neuroadaptations in Receptor Expression That Predispose to Addiction

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Abstract - The neuroscience of addiction is complex and involves a variety of responses. Addiction is a chronic, relapsing disorder that involves compulsive seeking of a stimulant to feel euphoria, despite the adverse consequences. It involves functional changes to brain circuits that are involved with reward, stress, and self-control. Anybody can fall into the trap of addiction, even elite athletes. This research addresses certain neuroadaptations in the striatum of the brain that renders elite athletes more vulnerable to addictive behavior, particularly because of an increased tolerance to dopamine and an elongated stress response, leading athletes to seek additional stimulation through risk-taking. The intense exercise of elite athletes can increase D2 receptor expression and binding in the striatum, until tolerance to the elevated levels of dopamine is eventually developed. At the same time, long-term endurance exercise can activate the stress response and stimulate the HPA axis and the SAM pathway, releasing cortisol. Activation of the stress response can push athletes to seek out abusive drugs or behaviors and makes them more vulnerable to the euphoric effects of the stimulant. Rodent studies revealed that reduced function of striatal D2 receptors can lead to diminished sensitivity to negative outcomes, since striatal D2 receptors facilitate avoidance learning. With diminished sensitivity to punishing consequences, athletes are more likely to take part in risky behavior in search of a dopamine rush. Risk-taking behavior can directly lead to a greater vulnerability to addictive behavior. In addition, low striatal D2 receptor expression represents a predisposing factor for risk-taking and subsequent substance abuse. Although athletes' personalities and genetics may predispose them to certain addictive behaviors, their lifestyle can certainly endanger them as well. With the relatively small availability of literature on this topic, this paper will review the literature to test the above hypothesis.

***Keywords*:** dopamine receptors, risk-taking, dopamine, exercise, tolerance, stress response

1. Introduction

The neuroscience of addiction is complex and involves a variety of responses. Addiction is a chronic, relapsing disorder that involves compulsive seeking of a stimulant to feel euphoria, despite the adverse consequences. Addiction involves functional changes to brain circuits that are involved with reward, stress, and self-control [22]. Anybody can fall into the trap of addiction, even elite athletes. According to the World Anti-Doping Agency, almost half of the athletes who took part in the 2011 World Championships in Athletics admitted to using banned substances [32].

This paper addresses certain neuroadaptations in the striatum of the brain that renders elite athletes more vulnerable to addictive behavior, particularly as a result of an increased tolerance to dopamine. Constant post-exercise increases in dopamine leads to tolerance and an elongated stress response, leading athletes to seek additional stimulation through risk-taking. Risk-taking behavior often includes the use and abuse of addictive substances.

1.1. The Striatum

The main reward circuits in the brain include the limbic system, the prefrontal cortex, and the basal ganglia, which includes the striatum. The striatum plays an important role in reward-related learning and consequently, the acquisition and maintenance of addictive behaviors. It is an area of convergence for inputs from various cortical areas and midbrain structures. The striatum comprises two types of gamma-aminobutyric acid (GABA)-ergic medium spiny neurons (MSNs): dopamine receptor type 1 (D1) and dopamine receptor type 2 (D2) [14]. The striatum receives dopaminergic inputs from the ventral tegmental area (VTA) and the substantia nigra (SNr). In addition, it receives glutamatergic inputs from areas including the cortex, hippocampus, and amygdala. The striatum can also be divided into two main regions: the dorsal striatum and the nucleus accumbens, or the ventral striatum.

The MSNs project in two main pathways, the direct and indirect pathways. The neurons in the direct pathway project monosynaptically to the globus pallidus internal (GPi) and SNr. In contrast, neurons in the indirect pathway project to the GPi and SNr via the globus pallidus external (GPe) and the subthalamic nucleus [35].

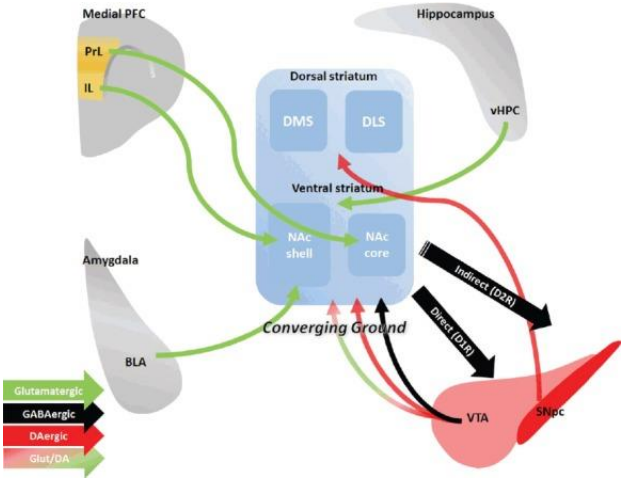

Fig. 1: An illustration of inputs to the striatum and the two direct and indirect paths of dopamine [14].

1.2. Dopamine Receptors

Dopamine receptors in the striatum are crucial to the addiction process. D2 receptors have a 10-to-100-fold greater affinity for dopamine (DA) than D1 receptors. Thus, it does not take much DA to activate the D2 receptors - they serve as an active baseline. D1 receptors on the other hand are stimulated by excessive levels of dopamine, typically as a result of unexpected events and drug use. They also have two different patterns of DA release: tonic and phasic firing. Usually, tonic firing of D2 receptors occurs, but in response to extraordinary rewards or particularly aversive events, dopamine neurons fire more quickly. Phasic firing results in a quick increase in DA which in turn activates D1 receptors. D1 receptors stimulate not only reward but also conditioning and memory mechanisms, involving the hippocampus, amygdala, and orbitofrontal cortex. The conditioning and memory processes are crucial to the development of addiction, as they help to associate a stimulus with a reward or punishment [31].

Typically, natural rewards only stimulate D2 receptors, as they produce a relatively low amount of DA compared to drug use and other unexpected events. Natural rewards involve activities such as sex, eating, and positive social interactions. These activities were considered important to survival in our evolutionary development and are thus sought by our brains automatically [4].

Since natural rewards only activate D2 receptors, they stay within a loop of satisfaction. D2 receptors diminish signalling from the ventral tegmental area (VTA), blocking activity of the stress response and opponent processes to produce satisfaction. In contrast, the D1 pathway activates a direct feedback loop that simulates more activity in the VTA and increases motivation in the prefrontal cortex, thus creating a continuous loop without any satisfaction [12].

1.3. Homeostasis and Allostasis

The brain is constantly working to retain homeostasis in the body. Homeostasis is a self-regulating process where biological systems maintain stability while adapting to external conditions. Even if the environment changes, an organism is still able to control and regulate its internal processes. The disruption of a homeostatic state can lead to a variety of diseases, including substance abuse disorders [2].

A departure from homeostasis is called an allostatic state. Allostasis is an adaptive process that maintains homeostasis via the production of hormones such as adrenaline and cortisol, mediating the stress response in unexpected departures from homeostasis. However, allostasis can also contribute to allostatic overload, which causes

someone to feel “stressed out.” For example, in an acutely challenging event, the brain will secrete the stress hormones adrenaline and cortisol to improve memory of the situation and avoid it in the future. Though, when stress is continuous, continuous, neuronal atrophy, or the death of neurons, can occur and memory of the event may be impaired [19].

1.4. The Stress Response

Hormones such as cortisol are direct results of the activation of the hypothalamic-pituitary-adrenal (HPA) axis, another phenomenon within the stress response that is activated by allostasis. The HPA axis is regulated by corticotropin-releasing factor (CRF). In response to physical and psychosocial stressors, the HPA axis activates a transient hormonal cascade that ultimately releases glucocorticoids, or cortisol in humans, from the adrenal cortex. Cortisol circulates in the bloodstream to release glucose and consequently mobilize energy.

Activation of the axis improves alertness to respond to challenging events for prolonged periods. The HPA axis also engages a negative-feedback circuit, where circulating glucocorticoids obstruct subsequent neuroendocrine responses. The amount of negative feedback is directly proportional to the amount of cortisol released from the axis [5].

Along with the HPA axis, the sympathomedullary (SAM) pathway is activated by short-term stress. The SAM pathway releases catecholamines including epinephrine and norepinephrine that regulate an immediate “fight or flight” response in the face of a stressor. This response optimizes bodily functions to manage the stressor [5].

1.5. Opponent Process Theory

The stress response is also linked to the opponent process theory. The opponent process directly counteracts the reward pathway and hedonic breaks with homeostasis. High levels of activity in the reward pathway will use excessive amounts of energy, so the opponent process attempts to counteract that and conserve energy. So, as the reward pathway continues to be stimulated, the opponent process begins to activate at the same time. Hyperkatifeia is rooted in the opponent process, which is an increase in the intensity of negative emotional states, typically involved in withdrawal from drugs. For both aversive and pleasant emotions and experiences, control mechanisms in the brain will serve as an emotional stabilization system to oppose departures from emotional neutrality.

The opponent process can also be divided into two distinct processes: the a-process and the b-process. The a-process is triggered after the initial use of a stimulant. It is a positive hedonic process and has a noticeably short time constant. The positive a-process then triggers the opposing b-process. The b-process reduces the hedonic intensity of the a-process and represents a negative emotional state. In contrast to the a-process, the b-process has a slow rise and decay. The negative b-process is strengthened with repeated stimulation through long-term potentiation, so that it has a faster onset, greater intensity, and takes longer to decay. Subjects may develop a tolerance to a specific stimulus, when it does not give off the same effect of euphoria after the activation of the opponent processes as before, since it is dulled by the b-process and hyperkatifeia [16].

1.6. Tolerance

After continuous usage of a stimulant, users can develop a tolerance to its effects, subsequently requiring more of the stimulant to experience the same “high.” A reduced sensitivity of the DA reward circuit and consumption of the reward is then developed, along with the increasing intensity of the stress response and opponent processes. This reduced DA signaling in response to rewards is also known as anhedonia [33]. Cravings for a stimulant and heightened DA levels also increase after tolerance and are rooted in the negative emotions of hyperkatifeia. Users seek pleasure in order to overcome the discomfort of hyperkatifeia [16].

2. Methods

The process of developing this paper began with establishing a general research question and direction. After developing the research question and initial thesis, the literature search began. The utilised keywords included general terms such as neurobiology of addiction, substance use disorder, street drugs, risk-taking, and addiction tolerance. These keywords resulted in 200, 8,000, 1,000, 4,000, and 200 results, respectively, on PubMed. These results came after applying the “free full text”

filter to ensure all complete articles were accessible. To comb through these sources in order to obtain a foundational background for the introduction section, the articles were filtered for the most relevant and recent articles based on their abstracts and other identifying information. They were also examined for the articles with the most "cited by" articles. is shown on PubMed and several other databases to delineate where else the article is referenced. For the next section paper, the main body of the literature review, the same methods were utilised except with varied keywords. For example, some search phrases that were used include exercise and addiction, athletes and addiction, exercise and dopamine, and After finding initial articles, the Snowball Method was used to find articles similar in relevancy and topic. Three main search engines were used: PubMed, the Oberlin College Database, and Google Scholar. In general, articles were filtered by analyzing the authors, publication date, content, and bias or limitations in their studies that would disqualify the articles from my reference list. There were no specific rejection criteria surrounding the nature of the article or study performed due to the relatively limited literature. However, for certain sections of the review, it was necessary to only search for certain types of articles. For example, the introduction called for mostly meta-analyses and other literature reviews, while the later section in the literature review itself necessitated more specific studies to pull analyses from. In these such articles, studies with large samples with a degree of diversity in demographic data were accepted.

3. Literature Review

Studies show that consistent, moderate aerobic exercise amplifies the availability and processing of dopamine neurotransmitters in the striatal region of the brain [3]. In MPTP-induced mice models of Parkinson's disease, intense daily exercise for 28 days (four weeks) resulted in higher levels of dopamine neurotransmission compared to non-exercise mice, through an increase in D2 receptor expression and binding in the dorsolateral striatum [24]. However, heightened activity during long-term endurance exercise can also activate the stress response [23]. Elite athletes experience physical and emotional stress during training that can lead to shifts in homeostasis, which stimulates the SAM and HPA axes [21]. The SAM system releases epinephrine to mobilize metabolic resources and regulate the fight or flight response. Similarly, acute physical exertion above 60% maximal oxygen uptake activates the HPA axis, which releases stress and catabolic hormones and improves alertness [5] [9]. Along with a stress response, athletes can develop a tolerance to the rewarding effects of exercise, as excessive increases in dopamine due to elevated levels of exercise can activate D1 receptors and kickstart the addiction cycle. Tolerance leads to increased risk-taking behavior to compensate for the decrease in D2 receptor expression [33].

Given the aforementioned research data, the central hypothesis of the paper is that elite athletes are more vulnerable to addictive behavior as a result of an increased tolerance to dopamine. Regular post-exercise increases in dopamine leads to tolerance and an elongated stress response, leading athletes to seek additional stimulation through risk-taking.

3.1. Increased Activity in the Reward Pathway

In both animal and human studies, intense and long-term exercise increased dopaminergic activity in striatal circuits that relate to the reward pathway. Though studies are inconclusive on the effect of exercise on dopamine (DA) receptors of healthy adults, studies revealed that exercise increases the availability of striatal DA amongst subjects with Parkinson's disease (PD) and methamphetamine use disorder [34]. By using a fast-scan cyclic voltammetry technique on mice, investigators reported that treadmill exercise increased stimulus-evoked DA release in MPTP-induced PD mice while also decreasing the decay of DA in the dorsal striatum. Additionally, positron emission tomography (PET) validated that treadmill exercise upregulates striatal D2 receptors [17]. These increases in dopaminergic levels due to exercise can consequently increase motivation for rewards.

Experimental evidence confirms that elite athletes who habitually complete the same set of exercises in practice feel high amounts of craving for reward due to higher activity in the reward pathway, even if the process for obtaining that reward entails risk-taking. In human models, subjects with more running experience felt increased motivational reward after running compared to those with less running experience who felt a decreased craving for reward [34]. In a study involving male rats, investigators reported that the rewarding effects of exercise are independent of exercise controllability. Male rats were assigned to locked wheels and either forced running (FR) or voluntary running (VR).

Both VR and FR groups saw increases in the activity of DA neurons in the ventral tegmental area [10]. This study shows that though elite athletes may not consistently be exercising voluntarily, like recreational athletes, they still experience increases in dopamine activity in the reward pathway.

However, increases in dopaminergic activity are accompanied by the activation of the opponent process, which is the is the stress response. Opponent process theory is a counteraction to the hedonic actions of addictive stimulants, which is is activated by breaks in homeostasis, called allostasis. For both pleasant and unpleasant emotions, control mechanisms in in the brain will work to re-establish emotional neutrality [16]. Typically, natural rewards such as exercise will run in a satisfactory loop with D2 receptors. Response to natural stimuli such as food and sex are determined evolutionarily important for survival and reproduction by the brain. It encodes survival advantages to respond to these stimuli and seek it again in the future. In drug addiction, abusive drugs hack this system to encode themselves as important to survival, so the brain automatically seeks them as well [13].

As D2 receptors are high-affinity, they do not require much dopamine to be activated; they have an approximately 10-to-100-fold higher affinity for DA than D1 receptors. Thus, the dopamine released through natural rewards is enough to stimulate these D2 receptors, but not the D1 receptors, which are low-affinity and require high volumes of DA to be activated. D2 receptors activate the indirect striatal pathway that inhibits signalling from the VTA and blocks the opponent process, establishing a satisfaction loop. However, as a result of the surplus of DA in the nucleus accumbens due to extensive exercise, D1 receptors may also be stimulated, activating the addiction circuit and the stress response [31]. When there is an unexpected event, such as an extraordinary reward, phasic firing of dopamine occurs, increasing DA levels and thus stimulating D1 receptors. D1 receptors activate reward and conditioning mechanisms, also enabling users to link a stimulus with a reward, establishing craving.

In fact, studies find that reversible-neurotransmitter-blocking inhibition of D1 receptors in the direct striatal pathway attenuates the conditioned place preference for a chamber paired with a good reward. On the other hand, inhibition of the indirect pathway fails to change food place preference [18].

3.2. Stress Response

Significant increases in DA levels within the striatal circuits will result in hedonic breaks with homeostasis, as they will increase the activity of the striatal circuits beyond homeostatic levels. As a result, the brain enters a state of allostasis, which requires the activation of the stress response to reduce the hedonic intensity of the initial process and re-establish homeostasis [16]. Allostasis is the process of maintaining apparent stability outside of the body's typical homeostatic range due to chronic stress. It represents a dysfunctional system that changes the reward set point [11].

The hypothalamic-pituitary-adrenal (HPA) axis consists of neuroendocrine pathways and feedback loops that maintain homeostasis and ultimately produce corticosteroids, or cortisol, the primary stress hormone [29]. In humans, studies show that physical exertion above 60% maximal oxygen uptake will stimulate the HPA axis and release stress hormones such as CRF [6]. Additionally, the chronic activation of the stress pathway and the HPA axis can lead to dysregulation of the system, which can result in an increased risk for immune system dysfunction, various mood disorders such as depression, metabolic disease, and cardiovascular disease [27]. Since elite athletes train and compete for hours on end, they will experience this harmful, elongated stress response that can push them to seek additional reward.

In addition, investigators reported that in mice, forced treadmill running induces stress, leading to increased anxiety and corticosterone levels. These increases were not detected in voluntarily running mice [30]. Elite athletes may also experience a similar increase in stress as a result of exercise because they are obligated to complete their training even if they do not want to do so - their career depends on it.

3.3. Tolerance

After the within system restores homeostasis by diminishing the expression of DA receptors, a tolerance to the DA released through exercise is cultivated. Tolerance to a stimulant is developed when a subject requires higher doses of the stimulant in order to feel its euphoric effects against the opponent process [16]. For example, reductions in the ability of cocaine to increase DA levels in the ventral striatum and produce euphoric effects have been observed in human cocaine

addicts, which leads users to ingest higher amounts (tolerance). In a study involving active male cocaine addicts and non-drug abusing male controls, methylphenidate, a drug with effects similar to those of cocaine, failed to increase DA in the striatum of cocaine abusers. Abusers would then be motivated to increase their consumption of cocaine, further amplifying their tolerance to the drug [33].

After tolerance to the natural reward of exercise is established in elite athletes, they require increased levels of raise activity in the reward pathway and experience the positive effects. Thus, athletes may seek additional stimulation through risk-taking. In fact, preclinical studies show that increased DA activity in striatal regions is associated with increased risk-taking [3].

3.4. Risk-taking Behavior

Craving for larger amounts of DA can be defined as sensation-seeking. Sensation-seeking is the willingness to take risks for the sake of experiencing exciting sensations. Behavioral psychologists have found that athletes tend to have greater levels of sensation-seeking traits. This is perhaps due to the increase in their tolerance to exercise-induced DA. In addition, sensation-seeking has been linked to a variety of risky behaviors, such as crime and substance abuse. Further, studies show that athletes are more likely to engage in hazardous drinking, particularly in the form of binge drinking [1].

Once tolerance to the natural rewards of exercise is established, dopamine receptor expression decreases to accommodate the increased dopamine in the system, leading users to require more exercise and dopamine to feel euphoria [33]. Rodent studies revealed that reduced function of striatal D2 receptors can lead to diminished sensitivity to negative outcomes, since striatal D2 receptors facilitate avoidance learning [7]. With diminished sensitivity to punishing consequences, athletes are more likely to take part in risky behavior in search of a dopamine rush.

In addition, studies have found that adults who make more risky choices after a reward on the Balloon Analogue Risk Task (BART) have lower striatal D2 non-displaceable binding potential than those who did not take as many risks [15]. In fact, rat models also showed that lower striatal D2 receptor expression is associated with more frequent risk-taking [28].

Risk-taking behavior can directly lead to a greater vulnerability to addictive behavior. For example, over the course of five days of consistent cocaine acquisition, risk-taking rats self-administered significantly more cocaine than risk-averse rats. Rats were characterized as “risk-taking” and “risk-averse.” If the rat consistently chose a small, safe food reward, they were classified as “risk-averse.” If they chose a more dangerous, risky food reward that is larger but includes the probability of a mild foot shock, they were “risk-taking” [20]. To add on, in a group of adolescents, subjects with potentially problematic substance use showed greater risk-taking and lower striatal activity compared to healthy subjects [26]. Thus, low striatal D2 receptor expression represents a predisposing factor for risk-taking and subsequent substance abuse.

3.5 Conclusion

Elite athletes’ tolerance to dopamine releases from exercise, a natural reward, may result in tendencies to seek risky behavior in order to compensate for the lack of euphoria from intense and long-term exercise. Thus, athletes may be predisposed to various addictive behaviors, from substance use disorder to gambling disorder, as athletes experience more of a craving for higher levels of DA that natural stimuli cannot offer.

4. Discussion

Through the research, the discovered evidence supports the aforementioned hypothesis that elite athletes are more vulnerable to addictive behavior. Through long-term, intense exercise, elite athletes become vulnerable to substance use disorders and behavioral addictions, mainly due to an increased tolerance to the dopamine released via exercise and a prolonged stress response, which leads athletes to seek additional stimulation through risk-taking to offset the lack of euphoria from natural stimuli such as exercise.

The intense exercise that elite athletes must complete on a day-to-day basis can increase D2 receptor expression and binding in the striatum, until tolerance to the elevated levels of dopamine is eventually developed [24]. At the

same time, long-term endurance exercise can activate the stress response and stimulate the HPA axis and the SAM pathway, releasing stress hormones such as cortisol [21]. Activation of the stress response can push athletes to seek out abusive drugs or behaviors and makes them more vulnerable to the euphoric effects of the stimulant.

Elite athletes across the globe suffer from intense physical and psychosocial stress, leading many down the dark path path of addiction. Studies estimate that 20-60% of athletes suffer from stress due to excessive exercise and inadequate recovery. Elite endurance athletes particularly suffer from this stress as they are training intensely for several weeks or or months consecutively, with little to no rest [6]. As a result, an athlete that needs to take a painkiller to treat an injury or is simply trying a stimulant out can be particularly vulnerable to becoming addicted to that stimulant because of their exercise-induced neuroadaptations. According to the World Anti-Doping Agency, 44% of athletes who took part in the 2011 World Championships in Athletics admitted to using banned substances [32].

The pressure and desire of elite athletes to constantly perform better and push their minds and bodies to absolute limits predisposes these extremely healthy individuals to severely dangerous and unhealthy habits. Many often think that the world of professional sports, with the athletes' healthy and luxurious lifestyles, is picture perfect. However, few realize the dangers that come with devoting one's life to sport and exercise.

In addition, athletes' mental health can be more fragile than common perceptions would lead one to think. Up to 35% of elite athletes suffer from mental well-being issues, from eating disorders to depression and anxiety [25]. Thus, it is especially important that athletes and aspiring athletes are aware of the risks implicated in the lifestyle and are properly equipped to handle the stress.

Though athletes are more vulnerable to addiction because of the aforementioned neuroadaptations, some athletes may simply be predisposed to addictive behavior because of their genetics and their personalities. For example, athletes who participate in sports with a higher risk for injury or death are higher in risk-taking than athletes in less dangerous sports. These risk takers have similar sensation-seeking profiles to those with substance use disorders, partly because of their sensation-seeking personalities [8]. Although athletes' personalities may predispose them to certain addictive behaviors, their lifestyle can certainly make them vulnerable to addiction as well.

This research draws on the scope of published literature to present a holistic view of how exactly intense bouts of exercise can lead one to take part in addictive behavior. In a world where the availability of recreational drugs and painkillers is incredibly pervasive, athletes who may believe they lead a healthy and clean lifestyle must be aware of the risks involved with exercise and addiction. Given that little is known about the predisposition of addiction, identifying vulnerable groups of people at risk to develop an addiction, such as elite athletes, can save many lives.

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