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Abstract

Modern science takes at face value the fact that exercise is beneficial for man's health. In recent years, medical health professionals have begun to harness exercise as a treatment for a broader range of maladies. Since various studies found increased exercise to correlate with higher levels of endorphins, most believed that the endorphins were directly responsible for what the vernacular dubbed "Runner's High." Scientists have sought to either augment or wholly disprove the endorphin hypothesis with further studies. Major Depressive Disorder, or MDD, is an affective condition affecting a significant portion of the general population. Aerobic exercise is increasingly being revealed to be an encouraging treatment for all types of depression and anxiety. The HPA Axis allows one to comfortably exercise without experiencing the extremely stressful symptoms that characterize psychological stress, such as depression, anxiety, fear, etc. Runners' High is the "…happiness, elation…inner harmony, boundless energy, and… reduction in pain sensation" that ensues following prolonged aerobic activity. Endorphins are the body's naturally occurring opiates. The Neurogenesis Hypothesis states that "a decrease in the synthesis of new neurons in the adult hippocampus might be linked to major depressive disorder." Further research implicates BDNF (Brain-Derived Neurotrophin Factor) in exercise-induced neurogenesis. The thought was that beta endorphins are what stimulate increased neurogenesis, in turn causing a decrease in MDD. β-endorphins are large molecules that are too bulky to pass through the BBB and therefore cannot be the cause any changes to occur within the brain. Researchers and scientists have thus turned their attention to endogenous endocannabinoids as the true source of analgesia, sedation, anxiolysis and reduced depression found in endurance exercisers. Chief ligand anandamide (AEA) engenders elevated levels of BDNF (Brain Derived Neurotrophic Factor) during exercise and return-to-baseline levels post-exercise. Endocannabinoids modulate nociception by affecting the Periaqueductal Gray system (PAG). Endogenous cannabinoids and exogenous cannabinoids (marijuana) act in similar fashions, leading to the addictive qualities of exercise. Compelling evidence has ascertained that endogenous endocannabinoids are the underlying cause of the many positive effects of aerobic activity.

Introduction

Modern science takes as face value the fact that exercise is beneficial for man's health. Hippocrates was known to say, "Even when all is known, the care of a man is not yet complete, because eating alone will not keep a man well; he must also take exercise..." While to a contemporary society this concept seems rather primitive and simplistic, it is a truth that forms the basis of modern health sciences. However, it has only been in recent years that medical health professionals have begun to harness exercise as a treatment for a broader range of maladies. Exercise is widely known to help keep one's weight down, tone muscles and enhance physical fitness. Scientists are perpetually expanding their knowledge of exercise and what kind of effects it has on the brain and the body's systems. An understanding of the neuronal activity, neurotransmitter actions and chemical releases that are the responses to varying degrees of exercise can be applied to treat disease and improve lives. One such application is exercise as a treatment for Major Depressive Disorder (MDD). MDD had previously been treated solely with antidepressants, but more recently is being dealt with using a combination of medication and exercise. Various case studies have undertaken to prove the relationship between exercise and positive changes in the MDD brain. Once the neuronal and chemical effects of exercise were established, it naturally led to the conclusion that depressive symptoms lessened due to a proliferation of certain positive hormones that were released into the brain in response to exercise. With further investigations, the popular conclusion was that the feel-good high associated with exercise is caused by endorphins, opioid hormones that appear to increase in response to exercise. Since various studies found increased exercise to correlate with higher levels of endorphins, most believed that the endorphins were directly responsible for what the vernacular dubbed "Runner's High." Since then, scientists have sought to either augment or wholly disprove the endorphin hypothesis with further studies.

Methods

The search engines used include ProQuest, EbscoHost, and GoogleScholar. Tributary information was also obtained using Wikipedia, the New York Times and WebMD.

Discussion

Major Depressive Disorder, or MDD, is an affective condition affecting a significant portion of the general population. In America today, about 5% of all people will eventually be diagnosed with MDD. Quality of life with MDD is radically impaired, and basic life functions such as eating, sleeping and maintaining personal hygiene can be affected. It has been found that roughly 10% of people diagnosed with MDD will probably commit suicide. This is all due to the overwhelming, pervasive feelings of severe depression that characterize Major Depressive Disorder. Deficits in executive function are also consequences of MDD. Patients tested with a Stroop Task, Go/No Go Task, Task-Switching Paradigm and Flanker Tasks all scored low in reaction times, indicating deficits in executive function ability (Ernst, et al. 2006). Previously, MDD had been treated solely with antidepressant medications such as SSRIs (selective serotonin reuptake inhibitors). The anti-depressant medication field is an ever-growing industry, despite limited success and many unwarranted side effects. For examples, anti-depressants stop

working after a while, since the body and brain become accustomed to the drug and gain a tolerance for it. In such a case, the dose would have to continuously be raised in order to have any effect. Furthermore, if one abruptly stops taking the dosage of medication, withdrawal symptoms such as "dizziness, loss of coordination, fatigue, tingling, burning, blurred vision, insomnia, and vivid dreams" may incur. Additionally, the patient may experience "nausea or diarrhea, flu-like symptoms, irritability, anxiety, and crying spells." This tendency is called the "Discontinuation syndrome" and is obviously best to be avoided. Other negative side effects might include insomnia, diarrhea and stomach aches, headaches, joint and muscle pain, reduced blood clotting capacity due to lowered concentration of serotonin in platelets and possible increased tendency towards violence and/or self-destructive behaviors. A Black Box warning was even issued in 2004 by the FDA against SSRIs, warning of the possible risk of "suicidal thoughts, hostility, and agitation in children, teens and young adults" (Harvard, 2019).

Between 30-35% of patients on medication do not even respond to the antidepressant treatment at all. The unpleasant side effects considerably compromise the patients' quality of life in many areas and make the medications undesirable as a primary treatment for depression. Furthermore, there is a high relapse rate found in patients treated with antidepressants, leading to a need for alternative and/or supplementary treatments (Blumenthal, et al. 1999).

Aerobic exercise is increasingly being revealed to be an encouraging treatment for all types of depression and anxiety (Heijnen, et al. 2016). A study was performed testing MDD symptoms in response to exercise. Participants were accepted for the study if they displayed depressive criteria as expressed in the DSM-IV and other symptoms such as "sleep disturbance, weight loss…psychomotor retardation or agitation, feelings of worthlessness or excessive guilt, impaired cognition…and recurrent thoughts of death." They also had to receive a score of at leave 13 on the HAM-D test. The HAM-D is a clinical rating scale used to measure levels of depression. Scores of thirteen to eighteen is mildly depressed, above 18 is severely depressed. Each of the subjects of the study were assigned to one of three groups – exercise treatment, medication treatment, and a combination of exercise and medication treatment. The assignment of groups was a randomized procedure to ensure that equally depressed participants were assigned across the groups. The exercise group met three times a week for 16 weeks, engaging in personalized exercise protocol according to their individual heart rate capability. The classes were overseen by a "trained exercise physiologist." The medication group was administered the SSRI sertraline, specifically used due to its "documented efficacy and favorable side effect profile." Dosages were administered by the staff psychiatrist at intermittent weeks. The combination group concurrently received the same medication and exercise regimens described above. Results were generally positive. Firstly, patients who engaged in exercise showed improvements in aerobic capability, with an 11% increase in the exercise group and a 9% increase in the combination group. Secondly, depressive symptoms improved equally across all three groups. Improvements on the HAM-D scores did not differ across groups, and neither did the scores based on DSM-IV depression criteria. "…The percentage of patients who were no longer classified as clinically depressed at the end of the 4-month treatment period did not differ across treatment groups." The only difference found that they patients benefited more rapidly in the combination group than did the patients in the exercise or medication groups alone. This study demonstrated that exercise treatment as an intervention for depression is equally as effective as medication treatment (Blumenthal, et al. 1999).

Numerous other studies, all of which sought to prove the efficacy of exercise have tested people who suffer from depression across the spectrum. One set of studies has shown that participants, ranging from young to elderly, who engage in daily exercise regimens are far less likely to develop MDD. Subsequent investigation further demonstrated that daily exercise improves depressive symptoms, even in people who have not been diagnosed with MDD. Exercise studies performed with healthy adults with no depressive symptoms also found positive results. These adults reported improved cognitive function, elevated mood and a general sense of well-being. One study tested how well exercise treated "moderate-to-severe" depression, concluding that the depression was highly improved. Another treated MDD patients with a combination of antidepressant medication and exercise regimens. A control group received medication and "health education" lessons. The medication/exercise group responded significantly better than the control group. Yet another tested a group of adults suffering from MDD, exercising with varying intensities of exercise. They found here that the most intense exercise group improved the most. A significant edge that exercise has over medication is that the effects of exercise may extend past the actual regimen, with the positive feelings enduring (in one study) up to almost two years past the experiment (Ernst, et al. 2006). This is in sharp contrast to antidepressant medication, of which the healing abilities curtail immediately with the end of dosage. This is why people on medication require concurrent therapy so that they can manage their life even after their medication dosage is over. On the other hand, exercise is found to be even superior to therapy itself in many instances, with various "young and middle-aged adults" positing that aerobic exercise helped their depressive symptoms more than therapies like psychotherapy, CBT and occupational therapy (Blumenthal, et al. 1999). Aerobic exercise performed by patients with depression and anxiety may improve cognitive function. (Heijnen, et al. 2016) Patients who scored poorly on various task functions, such as Stroop and Flanker Tasks, scored significantly higher following 30 minutes of aerobic exercise (Ernst, et al. 2006). All of these studies have consistently found lower MDD

and anxiety levels in response to exercise training, in addition to higher psychosocial functioning, increased positive affect and elevated mood (Blumenthal, et al. 1999).

The obvious question that troubles scientists and mental health specialists is why exercise has such a potent effect on the human psyche. While the physical action of aerobic exercise is known to cause weight loss and increased fitness due to burning of calories and fat and muscle toning, the reason behind the mental effects are not as simple to extrapolate. Exploring the neuroendocrine response that takes place in response to aerobic exercise may help to ascertain the underlying cause.

Exercise that activates the heart rate from its resting point and raises the maximum capacity of oxygen intake (VO2max) at least 60% can be classified as a physical stressor. In response to such a stressor, the hypothalamus secretes "corticotrophin-releasing hormone, which travels…to the anterior pituitary to induce adrenocorticotropic hormone (ACTH) release" into the general circulation. Arrival of this hormone at the adrenal cortex stimulates cortisol release into the bloodstream. Cortisol acts as an inhibitor and, through the use of medial prefrontal cortex (mPFC) receptors, inhibits "overexcitability of the amygdala" that naturally occurs when a stressor arrives in the bloodstream (Heijnen, et al. 2016). This stress response is known as the Hypothalamic-Pituitary-Adrenal (HPA) Axis, so named for the journey of hormones from the hypothalamus, through the anterior pituitary and into the adrenal cortex, causing relaxation from the body's increased stress levels (Blumenthal, et al. 1999). The elevated levels of cortisol can last up to 2 hours after the actual exercise action, and the amount of cortisol released is proportional to the amount of exercise. Equally important in the stress response is the inactivation of cortisol back into cortisone. This homeostatic cycle ensures that frequent exercisers do not suffer from extreme cortisol levels that can lead to "hypertension, hyperglycemia, major depressive episode and anorexia nervosa" (Heijnen, et al. 2016). Thus, ACTH is a regulatory mechanism that acts as the body's natural stress response. This allows one to comfortably exercise without experiencing the extremely stressful symptoms that characterize psychological stress, such as depression, anxiety, fear, etc. (Angelopoulos, 2001). However, while this neuroendocrine response accounts for the control of increased psychological stressors while exercising, it could hardly account for the flood of "euphoria, anxiolysis (reduction of anxiety), sedation, and analgesia (relief from physical pain)" that characterize what we call Runner's High (Reynolds, 2015).

Runner's high is the reason that America has its plethora of addicted runners clocking miles in their sneakers every day. Every athlete can describe the "…happiness, elation…inner harmony, boundless energy, and…reduction in pain sensation" that ensues following prolonged aerobic activity (Dietrich, 2004). This so-described high is experienced frequently by endurance athletes, but really by anyone who exercises profusely for an extended amount of time. Scientists have struggled for decades with the reason behind runner's high and many hypotheses have been debuted and disproven over time. For years the Endorphin Hypothesis was the most popular by scientists and the overall population, gaining strength through hearsay and seemingly impenetrable evidence.

Endorphins are the body's naturally occurring opiates. When a person exercises, these chemicals are released in the brain, seeming to improve the athlete's mood and promote endurance. While exercise is known to be a healthful practice to engage in for one's physical health, it can cause degrees of discomfort or even pain. Therefore, it would make sense that in response to exercise, endogenous opiates with antinociceptive properties similar to morphine would be released (Reynolds, 2015). Any kind of intense endurance exercise can induce endorphin release, and it seems that the greater the exercise, more mood-altering endorphins are proportionately released (Kolata, 2008). Endorphins are "cleaved from the preprohormone pro-opiomelanocortin (POMC)…a protein found in the pituitary gland and the brain" (Ernst, et al. 2006). The C-terminus of the POMC protein in turn gives rise to hormones such as opiate peptides.

In one experiment, researchers used PET (positron emission tomography) scans to compare endorphin levels in the brains of athletes. Ten athletes did a two-hour run and were tested for opiate levels before and after the run. Additionally, the runners took a psychological test pre and post-run, intended to measure their moods before, and in response to, the flood of endorphins. The researchers did find increased levels of endorphins attaching themselves to the limbic and prefrontal areas of the brain, zones typically associated with emotion. The athletes also reported higher mood and euphoria in a seemingly direct relation to higher endorphin levels in the brain (Kolata, 2008, Heijnen, et al. 2016). Technically, all this study proved was that there is indeed a flood of endorphins in the brain in response to exercise. While there seems to also be a correlation between the elevated opiate levels and mood, the proof was not – yet – impenetrable.

A study performed at the Iranian Academic Center for Education, Culture and Research (ACECER) attempted to ascertain how endorphin levels are affected due to exercise. The researchers included subjects with fibromyalgia (FM) as well as healthy patients. The study was based on the assumption that exercise increases release of endogenous β-endorphins, and that β-endorphins lessen pain perception. Exercise has previously been used as a treatment for diseases such as FM, with a strong role in nociception and elevated pain threshold. Specifically in FM cases, however, the "analgesic effect" or lessening of pain perception seemed significantly dulled. According to the results of the study, this would seem to be due to the fact that FM patients produce less β-endorphins as they exercise and therefore

are less capable of blocking pain. All of the subjects first rested in a supine position in order to attain their basal heart rate, a range of 60 to 100 beats per minute. Blood from the anti-cubital vein was drawn at baseline and at the end of the exercise test in order to compare β-endorphins levels. The exercise test was a treadmill routine that continued as long as the subject was able, until the onset of "fatigue, pain, or physical exhaustion". Every three minutes the incline of the treadmill as well as the speed increased according to specific intervals. As soon as 70% of the patients HRMax (maximum heart rate) was achieved, the subject was told to continue for 15 more minutes only, and their level of exercise intensity was recorded. The post exercise blood was drawn directly afterwards, when the heart rate was still at its maximum. The results were rather interesting. The mean exercise times for the FM and healthy groups revealed that it took a much shorter time for the FM subjects to achieve HRMax than the healthy group. The majority of subjects who were able to reach their HRMax at later stages of exercise were from the healthy group. Ninety three percent of the healthy group, as opposed to the mere 30% of FM subjects, reached HRMax during stage four of exercise. This indicated that FM patients were unable to exercise to the same extent that the healthy participants were. While the blood samples indicated that both groups had amounts of β-endorphins, the FM subjects has significantly lower levels in both their baseline blood and in the post-exercise blood. This means that while both groups experienced a rise in β-endorphins due to the exercise, the FM patients were unable to produce the same influx of β-endorphins as the healthy group. These blunted levels of β-endorphins may explain why FM patients are more immune to the analgesic effects of exercise that usually take over post-exercise. Usually, aerobic exercise stimulates elevated β-endorphins levels which in turn seem to stimulate decreased nociception, elevated mood and psychological stability. However, due to "failure of normal elevation of [endogenous] β-endorphins," FM patients seem less able to produce the same analgesic effects. Therefore, they might be more prone to develop chronic allodynia (pain from a non-painful stimulation of the skin) and heightened nociception with the absence of normal β-endorphins levels (Bidari, et al. 2016).

Scientists have explored how endorphin levels rise in response to exercise. A study sought to verify the elevated levels of endorphins, with and without naloxone (opiate antagonist). It has already been proven than exercise with an intensity of 75% of VO2max and 80% of HR (heart rate) causes an elevated release of beta endorphins into circulation. However, this study examined whether longer lengths of activity cause even further increased endorphin levels, and how long one must exercise to stimulate endorphin release. The study included "nine healthy, fit males." In this double-blind experiment, some subjects were injected with naloxone, and some with a mere placebo. They all took a graded exercise test (GXT) to assess their physical capabilities and then performed exercise on treadmills, running until they were too exhausted to go on. Phlebotomy techniques were used to draw blood and measure beta endorphin levels. Levels of VO2max, HR (heart rate) and hematocrit (ratio of RBC volume in blood) were measured during 10 min, 20 min and 30 min intervals for both trials. No changes in Hct levels were found between trials.

β-endorphin concentration across the trials were recorded and trials showed significant differences. Before exercise, β-endorphins levels were at roughly 40 ml; across 10, 20 and 30-minute intervals, influxes of 80 to 90 ml of β-endorphins were recorded. Of note is that after the initial rise in β-endorphins, the volumes leveled off and stopped rising across time during exercise - it stayed constant. β-endorphin levels were significantly higher under naloxone administration. To summarize the results of the study, a significantly large increase in β-endorphin were found during and throughout exercise as compared to resting levels. They also found that the men injected with Naloxone experienced even higher levels of β-endorphins. Additionally, tests with low to moderate levels of exercise showed no changes at all in β-endorphin levels. Therefore, this suggests that it is only intense aerobic exercise that induces significant increases in β-endorphins. This elevation occurs rapidly from the onset of exercise and remains level through the duration. This test found much higher β-endorphin levels in the naloxone-injected participants as compared to the placebo participants. However, other experiments did not find much of a difference between naloxone test and placebo test. This is an obvious disparity that may be due to "differences in the exercise protocol, method of administration of the antagonist, and in the stereo-specificity of the antagonist used in the respective experimental protocols" (Angelopoulos, 2001).

Now the question stands, what is it that causes this drastic β-endorphins rise during exercise? The researchers suggest that Naloxone attaches to the opioid receptor, blocking any other opiates and signaling the pituitary gland to release more β-endorphins. These β-endorphins do glucoregulation during exercise, "augmenting glucagon levels and attenuating insulin release." Glucagon keeps blood glucose at high enough levels to allow the body to function normally (Glucagon, Diabetes. Co). This is a positive feedback loop – more β-endorphin is released, it does more glucoregulation, and so more β-endorphin is released. This may be why endorphin levels were higher with Naloxone injections.

ACTH also increases under stressful condition, just like β-endorphins. ACTH is also secreted by the pituitary and regulates cortisol in the bloodstream. Just like the endorphins in this study, ACTH levels rise with an injection of Naloxone. Thus, it seems that both β-endorphins and ACTH are regulatory mechanisms, acting to ensure the body's homeostasis despite outside

stressors. However, ACTH regulates the psychological stress response and endorphins normalize the physical response. This study demonstrated how and why β-endorphins levels were significantly elevated over the course of aerobic activity (Angelopoulos, 2001).

It is clear that aerobic exercise indeed causes an influx of β-endorphins to be released into blood circulation. The next step would be to secure as fact that it is indeed the flood of endorphin opiates that lowers depressive symptoms and induces a euphoric affect. The following study attempted to ascertain the possible link between aerobic exercise and the subjects' emotional state. The study involved middle aged subjects engaging in physical activity. First off, the subjects' emotional states were evaluated using FaceReader. FaceReader is a facial analysis software that assesses emotional state based on 6 primary emotions - happy, sad, angry, disgusted, scared, and surprised. The subjects were also interviewed personally to assess how they were feeling just then. After the facial analysis the researchers drew blood from the median cubital vein of each subject to have a baseline sample of blood plasma levels. The physical activity was measured using a veloergometer load test. A veloergometer is similar to an elliptical exercise bike, however it is equipped with specialized hardware capable of measuring physical prowess. This exercise regimen is called a load test, and it commenced for a half hour, with increasing load every three minutes. After the load test, the pre-test procedures – FaceReader, interview and phlebotomy – were repeated and analyzed. The pre and post blood measures were tested for plasma beta endorphin levels to see if there was an increase in endorphins in response to the exercise. If an increase was accompanied by a similar increase in mood, this would provide evidence that it is endorphins that cause the elevated mood associated with physical activity. The results showed an endorphin increase in only half of the subjects. However, in regard to positive affect, the data found a general increase across the subjects. A 20% increase in happiness was found and all except one showed a decrease in negative emotions. (One subject showed an increase in disgust due to unpleasant lab conditions) (Kundzina, et al. 2014). These findings definitively supported the hypothesis that extended aerobic exercise of at least 60% VO2 intensity is directly linked to increased positive affect and decreased depressive symptoms. It is of significance to note, however, that only half of the subjects showed a marked increase in circulating beta endorphin levels. Here we introduce a hypothesis that closely allies with the subject at hand. This is the Neurogenesis Hypothesis, which states that "a decrease in the synthesis of new neurons in the adult hippocampus might be linked to major depressive disorder (MDD)." Anti-depressant medications such as SSRIs have been used for years as treatment for MDD. Anti-depressants act to stimulate synthesis of new neurons in the adult brain. Eventually, a link was drawn between the anti-depressants and neurogenesis, since the time it takes for medication to have an effect is the same span of time it takes for the newly synthesized neurons to gain functionality. Returning to our exercise hypothesis, an experiment with lab rats found a 2 to 3-fold increase in neurogenesis in rats who had "regular access to a running wheel when they are compared with control animals." This discovery naturally led to the awareness that exercise assuages depressive symptoms by inducing increased neurogenesis, the "growth of new neurons in the adult [mammalian] brain." While it was once thought that neurogenesis is limited to the developmental stages of growth, it is now known that certain areas of the adult mammalian brain retain active progenitor cells that are constantly synthesizing new neurons and glial cells. There are two major sites of adult neurogenesis, the dentate gyrus of the hippocampus and the subventricular zones adjacent to the lateral ventricles. Based on experiments performed with lab mice and rats, roughly 9,000 new neurons are synthesized daily in the dentate gyrus alone. Research indicates that these numbers are reflective of human neurogenesis as well (Ernst, et al. 2006). One site of adult neurogenesis is the subventricular zone (SVZ) that is adjacent to the lateral ventricles of the brain. "Numerous proliferative precursor cells" line the walls of the ventricles that are composed of ependymal cells. The precursor cells are contained in this zone and eventually mature into new neurons and glial cells. The second site is the dentate gyrus (DG), located on the hippocampus in the brain. The hippocampus, a "bilateral limbic structure that plays a role in…learning and memory...." has two distinct areas – the Cornu Ammonis (CA) and the dentate gyrus. The CA has three subfields filled with pyramidal cells, multi polar neurons that act as primary excitation neurons in the brain. The dentate gyrus is connected to the CA and is "composed of small, round granule cells" that form a C shaped area. It is underneath these granule cells that active progenitor cells are housed and give rise to new neurons and glia, giving the area its name – the subgranular zone (SGZ) of the dentate gyrus. The two zones are closely adjacent to each other but develop differently. Active progenitor cells in the dentate gyrus give rise to daughter cells that migrate into the granule layer above. There, they develop and send out axons into the Cornu Ammonis region 3 (CA3). Over the course of four to five weeks, these daughter cells mature and act like fully grown granule cells. The daughter cells in the subventricular zone give rise to daughter cells that migrate into the olfactory bulbs to act as local interneurons. Thus, there is adult neurogenesis occurring daily at a rapid rate in the healthy mammalian brain. The neurogenesis theory states that if this complex process should somehow be impaired and fewer neurons would be created, the result would be the expression of depressive symptoms. The introduction of anti-depressant medications would promote neurogenesis and get the brain back on track. The plot thickens with the discovery that exercise too, promotes neurogenesis in the hippocampus of the brain. This strongly links exercise as a reliable therapeutic intervention for treatment of MDD (Ernst, et al. 2006).

Several research experiments have sought to augment the proof with concrete data. Firstly, MRI (magnetic resonance imaging) data have shown that hippocampal volume is severely compromised in the brains of depressed patients. This would give strength to the idea that it is reduced neurogenesis in the dentate gyrus that gives rise to depressive symptoms. Other studies showed that the corticosteroids released from the adrenal gland as part of the natural stress response (HPA Axis) negatively impact neurogenesis in the hippocampus, thus causing the "decreased hippocampal volume associated with MDD." The stress response is thus amplified, sustaining a vicious cycle of continuous depression and stress response. It's important to note that the decreased size of the hippocampus is not due to the degeneration of pre-existing neurons. Therefore, it would follow that fewer neurons are being created in the first place. Comparatively, researchers found increased hippocampal volume in direct relation to aerobic exercise. Lab rats that engaged in aerobic exercise consistently displayed large increases in hippocampal volume due to subsequent supplementary neurogenesis. As compared to control mice and rats with no access to a running wheel, active mice displayed double the number of new neurons in the subgranular zone of the dentate gyrus of the hippocampus. Furthermore, it has been ascertained that treatments for MDD, such as SSRIs (selective serotonin reuptake inhibitors) or electroconvulsive shock therapy, also cause an increase in neurogenesis. This expresses a direct relationship between neurogenesis and lessening depressive symptoms. A third proof involves the timing. Newly generated neurons typically require four to five weeks to become fully functioning neurons. This is a "latency similar to the onset of therapeutic benefit for most…antidepressant medication[s]." This information also supports the idea that proper neurogenesis is integral to reducing depressive symptoms. Research has even shown that in certain cases, aerobic exercise can foster the same therapeutic effects as cognitive therapy (Ernst, et al. 2006).

Further research implicates BDNF (Brain-Derived Neurotrophin Factor) in exercise-induced neurogenesis. BDNF promotes "neuronal survival and regeneration" in the adult brain. Aerobic exercise causes elevated levels of BDNF to be produced specifically in the CNS. This specificity indicated that BDNF plays a particularly central role, namely in the brain. One study found that exercise in mice led to increases in BDNF. They also noted that in a case with depressed lab animals, exercise led to an increase in both BDNF levels and hippocampal neurogenesis. On the other hand, it is known that it is neurogenesis that causes the anti-depressant effects of exercise; therefore, it was concluded that elevated levels of BDNF contribute to increased neurogenesis, thus playing an indirect role in lowering the depressive symptoms. BDNF stimulates cell proliferation specifically in the subgranular zone of the dentate gyrus, and also supports long-term survival of these new neurons. A positive cycle can thus be recognized: exercise increases BDNF, BDNF enhances neurogenesis and neuronal survival, causing increased positive affect, probably leading to further exercise to prolong the effect (Ernst, et al. 2006).

The obvious question is: why does exercise stimulate neurogenesis; what endogenous substance causes the brain to up the ante on neurogenesis when the body is engaged in aerobic activity? This returns us to the endorphin hypothesis. The thought was that endorphins are what stimulate increased neurogenesis, in turn causing a decrease in MDD. Studies have found that not only do infusions of opiate peptides seem to cause an increase in neurogenesis in the dentate gyrus, but also that "opiate receptor antagonists" seem to cause a decrease in adult neurogenesis. Therefore, endorphins may have a role in the survival and/or formation of new neurons and glia (Ernst, et al. 2006).

The Endorphin Hypothesis seemed sound, and was sustained for decades in the medical arena and among lay athletes at large. However, significant holes in the hypothesis were sprung that threatened the authenticity of its claims. Among other problems, the most substantial issue was that of the Blood Brain Barrier (BBB). Blood Brain Barrier describes the precise "microvasculature of the central nervous system." It is a semipermeable border separating the blood circulation from the brain and ECF (extracellular fluid of the CNS). This system of tightly packed endothelial cells (in the capillary wall), astrocytes (covering the capillaries) and pericytes (embedded in the basement membrane of the capillaries) is able to control the movement of substances to and from the brain and blood circulation. Substances such as "molecules, ions, and cells" are screened heavily by the BBB to ensure that no harmful microbes or other destructive substances reach the brain. This system ensures proper neuronal function and protection of the brain and spinal cord against "toxins, pathogens, inflammation, injury, and disease" (Daneman, R, et al. 2015). Since the cells of the BBB are so tightly packed, certain molecules that are too large are unable to pass through to gain access to the Central Nervous System. An example of such large molecules are beta endorphins. They are too bulky to pass through the BBB and therefore cannot be the cause any changes to occur within the brain. So, while endorphins are indeed released during exercise and may staunch peripheral muscle pain that results from exercise, they cannot be the source of any Runners' High or diminished depressive affect (Reynolds, 2015, Fuss, et al. 2015, Dietrich, 2004). Other "methodological confounds" inherent in the endorphin hypothesis are as follows:

1. Firstly, the possibility of cross reactivity is very strong. Cross reactivity occurs when two antigens are very similar in their amino acid makeup and therefore an antibody raised against one antigen might also bear an affinity for the similar antigen. The antibody is "programmed" to find the first antigen but it also recognizes the second. Beta endorphins

bear almost identical amino acid sequences with adrenocorticotropic hormone (ACTH) and other pro-opiomelanocortins. Therefore, any detecting antibody would possibly cross-react, making it difficult to detect which is which. (Proteintech, 2018) This is a serious confound for scientific experiments involving the authentication of the beta endorphin hypothesis and possibly invalidates much of the proof presented from these experiments. The fact that endorphins have similar structure specifically to ACTH is a further confound, since ACTH is also known to increase with endurance exercise.

2. Furthermore, when beta endorphins bind to a μ opioid receptor, it activates the "endogenous opioid system" that further activates the "analgesic and euphoric properties" inherent in the opiate system. It is also known, however, that symptoms such as "severe respiratory depression, pinpoint pupils, and inhibition of gastrointestinal motility" are all characteristic of endogenous opioid activation (Dietrich, 2004). If it were beta endorphins that were activating the opioid system, these symptoms would also be present in runners and endurance athletes. Since they are not, we are forced to reevaluate what it is that truly causes Runners' High.

Endocannabinoids

Researchers and scientists have now turned their attention to endogenous endocannabinoids as the true source of analgesia, sedation, anxiolysis and reduced depression found in endurance exercisers (Dietrich, 2004, Heijnen, et al. 2016). More recent studies are focusing on endocannabinoids and what is it about them that makes exercise "mildly intoxicating" (Reynolds, 2015). Endogenous endocannabinoids are the body's natural chemicals that improve mood and reduce nociception. They are endogenous lipids that "engage cannabinoid receptors, producing analgesic and euphoric effects just like those of exogenous cannabinoids, namely marijuana (or cannabis - Δ-9-THC ((–)-trans-Δ9-tetrahydrocannabinol;THC) (Lu, et al. 2016, Reynolds, 2015). While we now know that opiate endorphins mediate analgesia on a peripheral level, we have seen that there are still analgesic effects that occur irrespective of a working opioid system. This supports the evidence that cannabinoid induced analgesia also takes place at a central level (Dietrich, 2004). Endocannabinoids are what tell the hypothalamus to induce the release of endorphins. Therefore, any analgesic effects that endorphins do have are actually mediated by endocannabinoids (Heijnen, et al. 2016). Unlike endorphins, endocannabinoids are small enough to cross the Blood Brain Barrier and bind to brain receptors, thus enabling them to induce peripheral as well as central effects (Fuss, et al. 2015). An interesting feature of cannabinoid function is that way they are produced. Classic neurotransmitters are created ahead of time and stored in their respective synaptic vesicles for whenever they might be needed. Cannabinoids, on the other hand, are created and released almost immediately on demand. When called upon, for example, by G protein coupled receptors or during depolarization, endocannabinoids will be "liberated in one or two rapid enzymatic steps and released into the extracellular space" to produce a rapid effect on the system (Lu, et al. 2016). There are two types of identified endocannabinoids, CB1 and CB2. CB1 can be found in the CNS, "densely concentrated" in the cerebral cortex, hippocampus, basal ganglia; amygdala, hypothalamus and cerebellum (Dietrich, 2004). Most CB1 receptors are found on axon terminals and pre-terminal axon segments, not on the active zones (Lu, et al. 2016). This further elevated endocannabinoids over endorphins, for while endorphins cannot even cross over in to the brain, endocannabinoids are located in the places one would assume pain relievers and analgesics would be found. The hippocampus is a site for memory, as well as neurogenesis which reduces depression; the amygdala regulates the fear response; the hypothalamus is the "master gland" of the brain and orchestrates all incoming and outgoing activity. The cerebral cortex is a massive conglomeration with numerous functions that would be affected by endocannabinoids. The frontal lobe of the cortex cares for "higher executive functions" such as "emotional regulation, planning [and] reasoning…" The parietal lobe is responsible for sensory integration such as touch, temperature and pain perception. Thus, is makes sense that these areas would abound with CB1 receptors. CB2 receptors are mainly located in the PNS, expressing themselves on immune cells, microglia and vascular elements to protect the CNS. (Lu, et al. 2016) There are also cb1 receptors on peripheral nerve terminals. For example, "pain sensing [small diameter] C fibers, large diameter Aß and Aδ fibers… [and] dorsal root ganglia" (Dietrich, 2004). Therefore, we see that ECBs are synthesized both centrally and peripherally, unlike endorphins which hare only synthesized in the Peripheral Nervous System. The possibility of a third cB receptor is currently being investigated and may turn out to account for some of the Runners' High effects.

Chief ligands of CB1 and CB2 receptors are anandamide (arachidonoyl ethanolamine) and 2-arachidonoyl glycerol (2-AG) (Lu, et al. 2016). They are derived from fatty acid derivatives. Anandamide is known to bind with cb1 receptors over cb2 receptors, indicating higher central activity over peripheral activity (Dietrich, 2004). Anandamide (AEA) is a "highly lipophilic" fatty chemical and therefore can easily cross in to the brain proper (Heijnen, et al. 2016). This would implicate anandamide in activating analgesic effects in the brain (Dietrich, 2004). AEA increased gradually when cortisol is released during the HPA Axis, demonstrating a role in regulation of stress and amygdalar over excitability (Heijnen, et al. 2016). Rats showed an increase in hippocampal anandamide after running on a wheel for an extended period of time, indicating that anandamide plays a role in exercise

and homeostatic regulation (Fuss, et al. 2015). Additionally, anandamide acts as a vasodilator and produces hypotension, facilitating blood flow during exercise (Dietrich, 2004).

Anandamide (AEA) also engenders elevated levels of BDNF (Brain Derived Neurotrophic Factor) during exercise and return to baseline levels post-exercise. As mentioned above, BDNF is part of the neurotrophin family and plays a strong role in exercise-induced neurogenesis. In addition to promoting positive affect due to neurogenesis, BDNF also "exerts beneficial effects on cognition through its ability to enhance neurogenesis, synaptic plasticity and long-term potentiation, the basis of learning." Therefore, enhanced release of AEA due to exercise stimulates BDNF to stimulate heightened cognition and learning. Indeed, psychological stress and mood disorders have been found to reduce BDNF levels in the brains of rats and mice. Physical stress, or aerobic exercise, does just the opposite. A study among an elderly population showed that "moderate intensity walking" over a year served to intensify BDNF levels, further causing task switching functioning to remain constant. The control group of sedentary elderly showed a diametric decline in BDNF and in task switching as well (Heijnen, et al. 2016). Other studies have shown that aerobic activity "ranging from 20 to 90 min of 40–75% of maximal power output or 40–60% of VO2max or 75% of maximal heart rate" causes noticeable increases in BDNF levels (Heijnen, et al. 2016). Thus endocannabinoids play a role in cognition and mood as well.

Scientists noted that there were elevated levels of both endorphins and endocannabinoids in the plasma of mice, post run (Reynolds, 2015). In one experiment, the cB receptors in mice were blocked, noticeably inhibiting the Runners' High that is usually induced post run. The mice were anxious and sensitive to pain perception. Blocking the endorphin receptors had no effect and the mice experienced the calming and antinociceptive effects of runners' high as usual (Fuss et al., 2015, Reynolds, 2015). A similar study also involved lab mice running in a wheel. First off, increased running directly increased levels of endocannabinoids, effectively inducing a reduction in anxiety and pain. Furthermore, ablation of the mice's cb1 receptors completely inhibited the runners' high effect, eliminating anxiolysis. When the mice were injected with blockers of their cB receptors, the analgesic effects were further inhibited (Fuss, et al. 2015). Yet another study with mice divided the mice into running and non-running groups. The running mice were at ease to spend more time in bright light areas, something anxious mice don't do. This indicated that the running induced sedation. The mice were also tested for pain perception with a hot plate test. The runners did not jump in pain or lick their paws as much as normal, indicating that running induced antinociception, endowing the mice with heightened "thermal pain sensitivity." All of these studies found that reductions in anxiety and elevated sedation in mice are due to increased CB1 receptors in forebrain GABAergic neurons, while antinociception was caused by cb1 and cb2 receptors in the PNS (Fuss, et al. 2015). This antinociceptive effect can even rival that of morphine (Dietrich, 2004).

Another study engaged healthy male athletes running at "varying degrees of intensity" over a period of four days. Each running session induced a 70-80% raise in basal heart rate, and was performed at 50-90% of maximal intensity capacity. A sharp increase in cB1 receptors was found in the "frontal cortex, amygdala, hippocampus, and…hypothalamus" all known to be essential areas that regulate affective homeostasis (Heijnen, et al. 2016). A similar study involved male college athletes exercising on treadmills or stationary bikes at 70-80% maximal heart rate. After about an hour, drastically raised levels of anandamide were measured in their blood circulation (Dietrich, 2004).

Another way that endocannabinoids modulate nociception is by affecting the Periaqueductal Gray system (PAG). The PAG serves an important role in modulating ascending pain transmission, fielding "afferents from nociceptive neurons in the spinal cord [and sending] projections to thalamic nuclei that process nociception." In regard to descending pain inhibition, the PAG inhibits neurons in the dorsal horn of the spinal cord. The major functions of the midbrain periaqueductal gray (PAG) include suppressing pain, fear and anxiety, and promoting analgesia and cardiovascular control" (Bebehani, 1995). "Electrical stimulation of [both] the dorsal and lateral periaqueductal gray system" causes not only bindings to cb1 receptors but a subsequent release of anandamide into circulation. Additionally, an experiment revealed that "subcutaneous injection of the chemical irritant formalin" caused a direct infusion of the ligand anandamide into the periaqueductal gray. This implicates anandamide as a nociceptive agent for central chemogenic pain (Dietrich, 2004).

Upon observation, it can be noted that runners' high is only found in response to endurance exercise, as opposed to exercise in spurts. Sports such as "sprinting…weightlifting…track, soccer, football, tennis [and] basketball" doubtfully engage the endocannabinoid system since they do not involve long term exertion (Dietrich, 2004). Running, dancing or biking are examples of activities that would engage the ECB system and induce a runners' high. As mentioned earlier, endorphins play a role in moderating only peripheral chemogenic pain in the muscles. In addition to the central effects of anandamide, we find that cannabinoids also act similarly to inhibit edema and muscle inflammation that might occur during intense exercise. This moderation is important for endurance athletes because muscle pain is a cause and effect of lactic acidosis, which in turn introduces symptoms like muscle ache, nausea and stomach pain (Dietrich, 2004).

Endogenous cannabinoids and exogenous cannabinoids (marijuana) act in similar fashions. "The psychoactive constituent of marijuana, Δ-(9)-tetrahydrocannabinol (THC), exhibits high affinity for the CB1 receptor, which is densely expressed in brain

regions implicated in the control of emotion and cognition." Therefore, just like marijuana, ECBs can induce sedation, analgesia, reduced anxiety, euphoria and even impaired spatial learning (Dietrich, 2004). This essentially means that prolonged exercise produces the same effects as marijuana.

This leads into the addictive quality of endurance exercise. The endocannabinoid system is closely linked with the dopaminergic reward system of the brain. Dopamine is the brain's pleasure hormone, and dopamine receptors D1 and D2 are modulated by endocannabinoids. The two main ECB ligands anandamide and 2-arachidonoylglycerol (2-AG) proliferate in dopaminergic pathways as a "retrograde feedback system" for GABA nerve terminals. There, they modulate dopamine transmission (Bloomfield, et al. 2016). Additionally, cBs affect dopamine activity by increasing firing rates in the medial forebrain bundle, ventral tegmentum and substantia nigra. In the same vein, withdrawing the cB presence would induce withdrawal symptoms similar to that characteristic of marijuana withdrawal. This is due to reduced firing of the pleasure hormone dopamine. Therefore, endogenous as well as exogenous cannabinoids (CB1) are what cause the influx of dopamine release into circulation, thus causing a feel-good high or a "Runners' High." Just like exogenous ECB cause drug addiction, so too endogenous ECBs engender an addiction to that which brings on the dopaminergic feelings, namely aerobic exercise. This explains exercise addiction; exercise causes elevated levels of ECBs, ECBs in turn cause increased firing of dopamine, inducing an addictive "high." Indeed, it has been found that even just blocking dopamine receptors inhibits Runners' High. Athletes who are forced to refrain from their routine endurance exercise (for example, in the case of an injury) report withdrawal symptoms not unlike those of drug withdrawal (Dietrich, 2004).

Conclusion

The analgesic, euphoric and anti-depressant effects that take hold in response to aerobic exercise have been a major source of contention among the medical, scientific and lay community for decades. The endorphin hypothesis certainly took center stage for quite a time as the source behind what the vernacular aptly termed "Runners' High." However, compelling evidence, experimental proofs and biological veracities have enabled scientists to ascertain that endogenous endocannabinoids are the underlying cause of the many positive effects of aerobic activity. Included in these positive effects are: elevated ACTH to regulate the stress response, heightened BDNF production to promote neurogenesis and neural survival, analgesia, anxiolysis, decreased anxiety and depression, euphoria, enhanced cognition, and numerous others. Endorphins do not cause Runners' High; however, they do engender other positive effects during exercise. Exercise has been seen to induce Runners' High in all ages and stages, be it depressed or emotionally healthy, young or elderly, and male or female. With this knowledge, the proof holds true that enhanced release of endogenous endocannabinoids due to aerobic activity reliably and consistently induces a Runners' High, and thus decreases the depressive symptoms inherent in Major Depressive Disorder.

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