Psychology Research and Behavior Management

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REVIEW

Potential Link Between Exercise and N-Methyl-D-Aspartate Glutamate Receptors in Alcohol Use Disorder: Implications for Therapeutic Strategies

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Abstract: Alcohol use disorder (AUD) is a significant risk factor, accounting for approximately 13% of all deaths in the US. AUD not only destroys families but also causes economic losses due to reduced productivity, absenteeism, and healthcare expenses. Statistics revealing the sustained number of individuals affected by AUD over the years underscore the need for further understanding of the underlying pathophysiology to advance novel therapeutic strategies. Previous research has implicated the limbic brain regions N-methyl-D-aspartate glutamate receptors (NMDAR) in the emotional and behavioral effects of AUD. Given that aerobic exercise can modulate NMDAR activity and sensitivity to alcohol, this review presents a summary of clinical and basic science studies on NMDAR levels induced by alcohol consumption, as well as acute and protracted withdrawal, highlighting the potential role of aerobic exercise as an adjunctive therapy for AUD. Based on our findings, the utility of exercise in the modulation of reward-linked receptors and AUD may be mediated by its effects on NMDA signaling. These data support further consideration of the potential of aerobic exercise as a promising adjunctive therapy for AUD.

Keywords: exercise, alcohol use disorder, AUD, NMDA receptors, brain, reward

Introduction

Alcohol use disorder (AUD) is a major risk factor for morbidity and mortality worldwide.[1] AUD refers to dysfunctional patterns of alcohol consumption that lead to clinically significant adverse symptoms of impairment or distress.[2] This seems to be a self-perpetuating problem as children growing up in families afflicted with AUD tend to develop depressive disorders, low self-esteem, and high levels of neuroticism later in life.[3] In the US, AUD is among the most prevalent mental health disorders.[4] Research since 2008 has found that alcohol-related harm is generally increasing among adults, particularly in women, based on the US national data that analyzed trends in alcohol-related harm such as hospitalizations over time.[5]

A cross-sectional study utilizing the CDC WONDER database estimated an annual 25% surge in alcohol-induced overall mortality among individuals aged 25–34 and 35–44 from 2018 to 2020. These numbers are likely not considering the implications of comorbidity with synthetic opioid-induced deaths during this time, as the above report only focused on the deaths ruled to be caused by alcohol, omitting polysubstance abuse.[6] Data collected from the US national panel between years 2015 to 2020 have found an upward deviation in 30-day drinking prevalence and binge drinking amongst individuals aged 25–30 during the COVID-19 pandemic. This longitudinal study had limitations regarding the validity of annual self-report data, retention of individuals throughout the study, and conflicting attribution to substance abuse.[7]

Received: 17 February 2024
Accepted: 16 May 2024
Published: 14 June 2024

Approximately 15% of children (0–17 years old) live in households with one or more adults diagnosed with alcohol abuse or dependence.[8]

Based on these statistics, it would be important to assess the high probability of onset alcohol use, especially in children and young adults.[9] The number of drinks consumed by youth (15 to 26 years of age) increases by 3% with each additional dollar per capita contributed to alcohol advertisements.[10] Early onset to alcohol (specifically before the age of 18) reduces educational attainment, which indirectly hinders lifetime labor market outcomes in society.[11]

Tolerance contributes to Alcohol Dependence (AD) which people sustain by consuming alcohol. Studies have found an association between alcohol abuse and dependence and domestic violence, fetal alcohol syndrome, economic cost, loss of productivity, and car crashes.[12] Multiple studies have shown the prevalence of participants aged 18–24 face a greater tendency to develop a tolerance for alcohol.[13] In the US, 12.5% of people depend on alcohol throughout the span of their lifetime, while 3.8% of people have identified having an annual dependence on alcohol.[14] Many individuals who engage in sustained alcohol consumption exhibit behaviors consistent with alcohol compulsion, which involves persistently consuming alcohol despite negative consequences. Clinical research on alcohol compulsion is limited due to ethical limitations, but studies utilizing rodent paradigms have been found to emulate brain-circuitry comparable to humans.[15] Alcohol Withdrawal Syndrome (AWS), is an array of physiological symptoms that result from secession of excessive alcohol consumption, constituting a component of AUD. AWS, due to excessive use of alcohol, can lead to impaired mental stability in people. This includes the prevalence of anxiety disorders, depression, and sleep disorders.[16] Symptoms of AWS can range from mild withdrawal symptoms to delirium tremens.[17] Signs may arise within 24 to 48 hours of last consumption, and symptoms could arise unexpectedly in an alcohol-dependent patient or by choice. In the most drastic cases, a patient may face delirium, and/or withdrawal seizures which may be fatal.[18–21] It is strongly advised that individuals seeking treatment for AUD undergo supervised detoxification due to the significant risk of severe physical symptoms during this phase. The American Society of Addiction Medicine (ASAM) recommends medication-assisted treatment to ensure a safe and medically supported transition through detoxification.[21] While pharmacological intervention has a statistically significant positive effect, studies have found medication used to treat AUD fail to consistently perform better than placebo in reducing AUD symptoms. Alternative non-pharmacological therapies like facilitation groups and Cognitive Behavioral Therapy (CBT) can be used to address maladaptive behavior patterns associated with AUD. However, studies have found the effectiveness of psychological interventions for AUD to have limited generalizability beyond specific controls and are no more effective than current pharmacological options.[22]

From a neurobiological standpoint, alcohol's mechanism of action is complex and involves a plethora of neurotransmitters including dopamine (DA), where even the anticipation of alcohol consumption is enough to illicit neurotransmitter signaling effects.[23–28] Other neurotransmitters involved in alcohol consumption include glutamate,[29–39] and γ-aminobutyric acid (GABA),[26,27,40–43] as well as glycine receptors (GlyRs),[44,45] serotonin[46–48] and the peptide hormone vasopressin.[49,50] It is well-known that opioidergic mechanisms are also linked to ethanol neurochemical induced neurological insults.[51,52] Given the notable differences observed during ethanol consumption, it is worth mentioning these neurotransmitters as they may play an important role. The gut microbiome is linked to a bidirectional signaling network between the enteric nervous system (ENS) and the central nervous system (CNS), forming the gut-microbe-brain axis. The dysfunction of the gut-brain axis contributes to cognitive dysfunction and mood changes seen in AUD-induced neuropsychiatric disorders. Imbalance in intestinal flora can lead to dysfunction in the gut-limbic circuit system, involving the hippocampus, amygdala, and frontal cortex.[53] The clinical manifestations of brain damage resulting from chronic alcohol use are primarily attributed to the pathophysiology stemming from thiamine deficiency. Due to the close association between alcohol consumption and thiamine deficiency, recurrent episodes of subclinical thiamine deficiency may play a role in the development of neurological conditions such as alcohol-related brain damage (ARBD), Wernicke encephalopathy (WE), and Korsakoff syndrome (KS).[54]

Research has revealed the profound effects that physical exercise has on neuronal proliferation, protein activation, and expression throughout the brain which includes hippocampal neurogenesis in humans.[55] There is a multitude of exercise regimens that illicit different physiological and neurobiological responses. This can be addressed by considering the difference between aerobic and anaerobic physical activity. Aerobic exercise is found to enhance brain plasticity and brain-derived neurotrophic factor (BDNF) levels while anaerobic exercise may have indirect benefits on mood and

cognition through overall fitness improvements.[56] In older adults, aerobic exercise training correlates with improved memory function and increased hippocampal tissue volume.[57] Research conducted on humans demonstrated the precise impact of aerobic exercise to increase regional brain metabolism in areas responsible for memory, motivational drive, motor processing, somatosensory processing, and cognition.[58] In both humans and animals, physical activity has been found to dampen physiological and psychological responses to stressful stimuli.[59] Additionally, exercise has been shown to have beneficial effects in alleviating symptoms associated with Parkinson's disease, Alzheimer's disease, stroke, substance use disorder (SUD), and reward deficiency syndrome.[60] Feelings of euphoria can also be elicited by physical exercise through the release of endocannabinoids and opioids. Neuromodulators like brain-derived neurotrophic factor (BDNF) to be highly active due to physical activity.[61] It is important to note the beneficial effects of exercise differ depending on various factors like biological sex differences, duration of physical activity, intensity of exercise, and genetic predisposition which warrants further research to explore the full potential of physical activity in mediating the effects of SUDs. Such factors impact the degree of efficacy and beneficial impacts exercise has on one individual versus the next. In addition, the various methods of evaluation and assessment of biological impacts of exercise can explain for the heterogeneity in results.[60,62]

Ultimately, the long-lasting negative impact AUD has demonstrated on a societal level highlights the pressing need for effective therapeutic interventions. Acknowledging the elevated recurrence of AUD despite pharmacological and behavioral therapies underscores the pressing demand for novel therapeutic strategies. Given the growing efforts instigating physical activity acting as a regulator of neurotransmitter systems and neurogenesis implicated in substance use disorders, there is an opportunity to explore the therapeutic potential of exercise on AUD. While NMDA receptors in the cerebral cortex and hippocampus garner attention in research, this review predominantly focuses on the hippocampus due to its crucial role in memory formation and the implications of AUD. It is important to recognize NMDARs role in various cognitive processes distributed across multiple brain regions, but the emphasis on the hippocampus in NMDAR research can be attributed by its disease prevalence and memory formation functions. By targeting neurobiological mechanisms and dampening the effect of alcohol induced neurotoxicity, exercise may offer a promising adjunctive therapy to complement existing treatment protocols for AUD.

The N-methyl D-aspartate receptors (NMDARs) play a major role in memory and synaptic plasticity. In the brain, NMDARs are found to be targets of alcohol consumption, although the exact action of ethanol inhibition of these receptors stands to be unclear.[63] Focusing on the synaptic cleft, utilizing ethanol for acute treatment of neurons shows no effect towards the presynaptic compartment. Conversely, the post synaptic department portrayed depressed currents mediated via NMDARs due to acute exposure to ethanol.[64] Contributing to suppressed NMDA activity, initial exposure to alcohol inhibits the action of glutamate on NMDAR in the hippocampus.[64] One experiment looked at hippocampal neurons with a voltage clamp utilizing ethanol concentrations of 5mM to 100mM to examine NMDA receptor activity and intoxication levels. The data from this study shows ethanol concentrations increasing from 5mM to 100mM correlating with a rise of inhibition of NMDAR hippocampal neurons[64] (Table 1). Studies have drawn the correlation of increased NMDAR inhibition due to high ethanol potency being related to the increased potency of ethanol intoxication in humans.[39] Few studies have shown implications of ethanol-mediated-NMDA inactivity attributed to the presence of C-terminal amino acids; while others attribute this phenomenon on the phosphorylation state of NMDAR subunits.[65–67] While mechanisms remain unclear, ethanol is found to limit the passage of cations through the NMDAR pore. This leads to a reduction of glutamate neurotransmission and further supports the concept of ethanol acting as a non-competitive NMDAR antagonist.[68] Although the nature of mammalian ion channel functionality in response to ethanol exposure is inconclusive; there is viable proof showing the linear relationship of NMDA depressed activity due to intoxicating levels of ethanol.

Contrasting the acute effects of ethanol on NMDARs, chronic use of alcohol is believed to trigger a compensatory mechanism by increasing levels of NMDARs in the brain.[74] The extended use of ethanol contributes to the down-regulation of GABAa receptors, while upregulating NMDARs involved in glutamatergic pathways.[75] The neurotransmitters linked to reinforcing effects of alcohol are said to be endogenous opiates, GABA, serotonin, dopamine, and glutamate acting on NDMA receptors.[76] There have been numerous studies that found chronic ethanol exposure increases expression of NMDARs in the hippocampus;[77,78] medial orbitofrontal cortex;[77] agranular insular cortex;[79] nucleus

Table 1 The Effects of Ethanol Consumption and Exercise on NMDA Receptors Found in the Hippocampus of Sprague-Dawley Rats

Test Conducted	Administration Method	Evaluation Method	Effect on NMDARs	References
Acute Ethanol Exposure	5mM of ethanol was placed on mature neuronal culture for approximately 40 seconds (no added Mg^{+2})	Whole-cell patch clamp recordings taken at −50mV	↓ function of NMDARs	[69]
Chronic Ethanol Exposure	14 day-exposure to 6% ethanol in a nutritionally complete liquid diet	SDS-PAGE & Western blot	↑ NR1 & NR2 protein levels	[70]
Ethanol Withdrawal	Transverse tissue slices were exposed to 75mM of ethanol for 6 days and then placed on withdrawal for 24 hours	Propidium iodide (PI) labeling	↑ function of NMDARs	[71]
Anerobic Exercise	Resistance wheel running (100g), running 5 km/night for 7 days	cDNA microarray, RT-PCR, and RNase protection assay	↑NR2A mRNA expression	[72]
Aerobic Exercise	Voluntary wheel running ~ 4 weeks	Voltage clamp inducing receptor-mediated fEPSPs, Q-PCR, Immunohistochemistry	↑Nr2B mRNA expression	[73]

Notes: This includes relative activity/function. All results comprise studies done on Sprague-Dawley rats aged 1–13 weeks.
Abbreviations: NMDARs, N-methyl-D-aspartate receptors; NR1, NR2, NR2A, and NR2B, subunits of the NMDA receptor; SDS-PAGE, Sodium Dodecyl Sulfate-Polyacrylamide Gel Electrophoresis; cDNA, complementary DNA; RT-PCR, Reverse Transcription Polymerase Chain Reaction; RNase, Ribonuclease; mRNA, messenger RNA; fEPSPs, field excitatory postsynaptic potentials; 1-PCR – quantitative polymerase chain reaction.

accumbens core; central nucleus of amygdala;[80] and other parts of the central nervous system.[81] It is important to note this compensatory mechanism has been shown to proliferate NMDARs that deviate from the endogenous receptors. For example, research done on animal models have attributed the increase of glutamatergic activity due to chronic ethanol consumption to novel NMDARs containing GluN2A and GluN2B subunits.[82] In addition, selection of alcohol-preferred rats (P rats) showed with chronic and intermittent alcohol exposure, protein levels of NR2a & NR2b increased in the nucleus accumbens core.[80] Utilizing various methods of electrophysiological and biochemical techniques found chronic ethanol exposure is shown to enhance the response of NMDA stimulation in the cerebellar granule, hippocampal, and cortical neuronal cultures.[83] While human studies remain limited when evaluating NMDAR composition, clinical studies in 2021 by Patel and others have put forth the initial test to consider upregulation of central striatal GluN2B subunit levels in individuals positive for familial alcohol use disorder.[84] Moreover, research has found single nucleotide polymorphisms (SNPs) in the Fyn gene of humans to impact the risk and severity of AUD.[85] Putting aside the effects shown in the hippocampus of rats/mice, an experiment conducted showed the effects chronic ethanol exposure may have on NMDARs found in the posterior cingulate cortex (PCC). Results show juvenile rats experiencing an increase in ethanol sensitivity by the neurons found in the PCC. This questions the sheer efficacy of learning and memory in young individuals who chronically drink alcohol.[86]

Excessive glutamatergic neurotransmission is known to be correlated with acute withdrawal syndrome (AWS) and a signaling factor for dependence-related neuroplasticity. One study showed a significant increase in glutamate levels during withdrawal in prefrontal regions of the brain, in addition to an increased glutamate/glutamine ratio.[87] Withdrawal symptoms faced by abstinence from chronic alcohol intake may be related to increased synthesis of glutamate and decreased synthesis of GABA in the brain.[88] Hyperactivity of the glutamatergic system due to alcohol withdrawal and the use of drugs impacting NMDARs has been linked to evident aggressive behavior.[25] In addition, AWS is greatly related to withdrawal-induced anxiety due enhanced function of NMDA receptors.[89] The protein levels for NR2A and NR2B subunits were elevated in the CA1 region of hippocampal slices from rats facing withdrawal from a chronic intermittent ethanol treatment.[90] In addition, alcohol withdrawn rats displayed downregulation of NR2B mRNA in the hippocampal region of the brain.[91] This increase in protein levels yet decrease in mRNA expression of the NR2B can be due to the initial upregulation of the mRNA when chronic ethanol exposure is taking place. Studies have found neurons perceptive to glutamatergic excitotoxicity after facing a period of ethanol withdrawal. This is further understood by NMDAR

activity since the use of MK801 (NMDA antagonist) during periods of abstinence is found to decrease ethanol-induced neurotoxicity.[64]

Effects of Exercise on Alcohol and Drug Use

Effects of Exercise on Drug Use

The number of studies evaluating the mechanisms of exercise reward pathways and the therapeutic effects against substance use is growing. For instance, aerobic exercise has been associated with diminished heroin craving in humans, and voluntary physical activity has been effective in reducing heroin-seeking behavior in rats, revealing the potential implications of voluntary physical exercise and therapeutic methods for heroin dependence in a clinical setting.[92,93] Additionally, studies have demonstrated that treadmill exercise can induce a brain glucose response in regions relevant to addiction behaviors, although the scope of some studies may be limited to specific conditions or populations.[62] Randomized controlled trials have linked acute moderate to vigorous-intensity exercise to decreased drug cravings in individuals with SUDs, highlighting the potential protective role of exercise against drug use.[72] While past research has explored exercise's impact on drug relapse, recent systemic reviews have emphasized exercise as a valuable component in SUD prevention, reduction, treatment, and recovery efforts. Overall, exercise has shown promise in alleviating symptoms of anxiety and increasing abstinence rates among individuals facing substance use disorders.[94–99]

Effects of Exercise on Alcohol Use

Research has revealed the profound effects that physical exercise has on neuronal proliferation, protein activation, and expression throughout the brain. Physical exercise is found to stimulate adult hippocampal neurogenesis in humans. This growth avoids intrusion between newly learned memories and established ones.[100,101] Aerobic exercise is found to elicit a "good stress" response throughout the nervous system. After the hypothalamic-pituitary-adrenal axis is stimulated, elevated cortisol levels in the circulatory system can inhibit the hypothalamus and pituitary gland through receptors found on the medial prefrontal cortex. This circuit reduces the excitation of the amygdala due to a stress response.[102] Studies have found acute physical activity to modulate levels of neurotransmitters like serotonin, norepinephrine, and dopamine. In addition, feelings of euphoria can be elicited by physical exercise through release of endocannabinoids and opioids. Neuromodulators like brain-derived neurotrophic factor (BDNF) can be highly active due to physical activity.[103]

Exercise regimens are increasingly being used as a means of intervention for individuals facing AUD.[104] A systematic review published in the United Kingdom aimed to discuss the literature available pertaining to the implications of physical activity in conjunction with alcohol and drug use across the lifespan. Findings therein point to exercise intervention in alcohol treatment being considered the most well-researched subject matter compared to prevention and reduction of alcohol use. In addition, meta-analysis determined exercise intervention posing no risk to alcohol and drug use. The various studies evaluated postulate the effects of physical activity being utilized for intervention and having a dose-dependent response to subjects participating in the research. This poses the idea of evaluating individuals seeking treatment based on basal physical activity levels, an (accompanied with an) acclimated level of drug use.[69] A randomized controlled trial evaluated the change in alcohol consumption in individuals aged 18–75 diagnosed with AUD who participated in exercise as a sole method of intervention, versus telephone counselling with a psychologist or a behavioral scientist. After the 12-week study was complete, results show aerobic exercise to decrease weekly alcohol consumption in comparison with usual treatment (ie telephone counselling). This particular study is limited to including participants seeking non-pharmacological treatment for AUD in which they would take part in a novel exercise protocol. The results can be dependent on the motivation to seek lifestyle changes and the ability to acquire access to exceeding treatment options. Nonetheless, this study did take into account basal physical activity of participants, excluding members who were already participating in regular physical activity.[105] A meta-analysis conducted in 2017 explored the possible health outcomes of exercise on individuals with AUD. Results show a significant decrease in depressive symptoms and improved physical fitness.[104] While one may be inclined to agree with the favorable effect of physical activity in preventing alcohol and other drug use, it is crucial to acknowledge the limited clinical data available to support this statement. According to Thompson and others, the area of using physical activity to

prevent alcohol and other drug use is relatively under-researched, with only five identified studies conducted in the USA.[69] When interpreting mechanisms on a micro level, glial cells are found throughout the adult nervous system and contribute to supportive functions of neurons that are essential to life. Alcohol exposure can result in a loss of glial cells which can allow neurodegeneration to occur. Research has found consistent data supporting the trend of increasing the release of tropic factors by microglia via physical activity.[106,107]

Effects of Exercise on NMDA Receptors

The glutamate system is crucial for processing information in various neural networks found in regions like the hippocampus or caudate-putamen.[108,109] Proton magnetic resonance spectroscopy (MRS) before and after intense exercise show signals for glutamate increasing in the anterior cingulate cortex, as well as the visual cortex.[110] Past studies looked into intervention methods for the highly active corticostriatal glutamatergic neurotransmission correlating to Parkinson's Disease. Physical activity was found to decrease the excessive glutamate activity by modifying metabotropic receptors such as NMDA and AMPA; all while not directly impacting dopamine levels.[111] Research done pertaining exercise restoring endogenous glutamatergic systems is important to consider when discussing the therapeutic methods used towards SUD intervention.

The literature devoted to evaluating the effects physical activity has on NMDARs focusses heavily on long-term potentiation (LTP) in both clinical and preclinical studies. A systematic review found studies which show acute and chronic engagement of physical activity having a robust effect on LTP in the brain.[112–115] There are several contributing growth factors and signaling mechanisms that play a pivotal role in the activity of NMDARs during exercise. The activation of NMDARs due to physical activity attributes to the enhancement of BDNF-mediated plasticity via signaling cascades which plays a huge role in the cognitive benefits derived from exercise.[60]

Evaluating subunit expression and relative activity of neuronal receptors during physical activity is found to be a prominent method of evaluation when assessing the beneficial effects of exercise against drug addiction. Research conducted to evaluate the effects of chronic aerobic exercise found change in only GABA(a) receptor activity compared to mu-opioid receptors.[116] In addition, one study attempted to assess the alterations of the mesolimbic dopamine pathway due to exercise, and how this may explain the changes in drug-seeking behavior. Results showed exercise rats displaying changes of dopamine-receptor binding in the ventral striatum and subregions of the dorsal striatum compared to sedentary rats. This may contribute to the neuronal mechanism responsible for reducing drug-seeking behavior. This study did not consider rodent sex differences that can ultimately impact dopamine-related measures during the experiment. Nonetheless, this type of study can allow a hypothesis that mechanistic alterations due to exercise that can serve a therapeutic advantage towards SUD.[117] We can also assess neurobiological receptors and systems to rule out possible mechanisms from physical activity that attribute to therapeutic methods against SUD. For example, the CB1 receptor plays an essential role in endocannabinoid signaling throughout the nervous system. One study evaluated CB1 receptor levels in the brains of chronic aerobic exercise rats. Results showed no significant alteration of CB1 receptor levels in exercise subjects. So studies utilizing the same exercise regimen can discredit the involvement of CB1-receptor level modulation in decreased drug seeking behavior.[118] The upregulation of the NMDA NR2B subunit in the hippocampus of rats was shown following low-intensity treadmill running for 8 weeks.[119] Long-term exercise protocols have been found to increase NMDA subunit expression, but acute high-intensity exercise (no longer than 30 minutes) does not induce the same effect.

Implications of NMDA Receptor Modulation of AUD Through Exercise

Effects of Exercise on AUD

There are several pharmacological therapeutic approaches of treating AUD that are proven to be successful for some. These include disulfiram, naltrexone, and acamprosate, which is believed to act as a noncompetitive NMDAR blocker.[71,120] In addition, non-pharmacological treatments like cognitive-behavioral therapy been effective in treating AUD.[70] Unfortunately, rates of relapse are still substantially high, which is concerning considering that almost 15 million Americans suffer from AUD.[73] In general, physical exercise can provide gratifying emotional states to participating

subjects. Exercise can mediate alcohol withdrawal, improve self-efficacy[104] and reduce alcohol dependency, as well as decrease relapse in subjects.[121]

Neurobiological Mechanisms

Neurogenesis has been shown in the hippocampus of exercise subjects.[122] Several molecular neurotrophic and growth factors come into play when investigating these effects of physical activity on the brain. This includes insulin-like growth factor-1 (IGF-1);[119] neurotrophin-3 (NT-3);[123] brain-derived neurotrophic factor (BDNF);[124] fibroblast growth factor 2 (FGF-2);[125] and vascular endothelial growth factor (VEGF).[126] Many studies looking into the protective effects of exercise against neurodegenerative diseases found IGF-1 to be responsible for broad c-Fos expression in neurons, in addition to improved memory performance after physical activity.[119] VEGF has shown to be a necessary component of adult hippocampal exercise-induced neurogenesis.[126] BDNF is considered to play an essential role in cognitive ability since low levels of it are recorded in patients suffering from neurodegenerative diseases.[126,127] Equally critical are the signaling pathways governed by these growth factors. Shifting focus to the hippocampus, we can gain insight into the neurobiological signal transduction during voluntary physical exercise. Such understanding extends to how physical activity influences AUD at both macro and micro levels. This pertains to the overall behavioral changes seen in clinical trials, to the mechanistic alterations that allow an individual to reap the benefits of exercise. The hippocampus has been extensively evaluated in research pertaining to AUD, which is relevant when evaluating the cause of impaired processing and memory formation displayed during intoxication.[128] These findings support examining NMDA receptor modulations pertaining to the neurobiological mechanisms within the hippocampus and the effects induced by alcohol exposure.

NMDA Receptor Effects in Different Alcohol States

Acute Exposure

Generally, research supports acute exposure to alcohol having a debilitating effect on NMDARs (Table 1). Specifically, a decrease in NMDAR function in hippocampal neurons due to the acute exposure to ethanol has been described.[129] In contrast, some studies have found evidence of increased NMDAR function due to acute ethanol exposure. Nonetheless, these studies acknowledge acute ethanol-induced inhibition of NMDARs with subsequent increase in receptor function due to NR2B tyrosine residue phosphorylation. Therefore, ethanol intake highlights the acute tolerance of hippocampal NMDARs due to phosphorylation.[130] Alternatively, the NR2A subunit and its associated protein kinases exhibit the opposite effect of NR2B due to ethanol exposure.[131] This study determined acute ethanol exposure indirectly prevents phosphorylation of the NR2A subunit.[132] Nonetheless, the compartmentalization of NR2B exemplifies a model of plasticity of these NMDARs that can determine the degree of sensitivity set forth if ethanol exposure becomes chronic.[133,134] Acute ethanol exposure is found to modulate motivational systems that ultimately allow the positive reinforcing effects of alcohol to occur.[135] Overall, research has shown in vitro analysis of acute ethanol exposure to decrease the activity or inhibit the functionality of NMDARs in various regions of the brain.

Chronic Exposure

Chronic alcohol exposure studies have reported a decrease in NMDA receptor function.[64,86,136,137] One key point is the variability of chronic exposure for ethanol exposure in vitro and in vivo varies. Historically, an increase in receptor subunit levels (NR1 and NR2A-B) in the hippocampus of rats was found following chronic ethanol treatment (Table 1). This can be an adaptation of neuronal cells in order to maintain homeostasis being that NMDARs initially decrease functionality due to acute exposure. The composition of these receptors plays a critical role in ethanol. Furthermore, chronic ethanol exposure tends to increase NMDAR synaptic transmission via elevated calcium influx.[137] The enhanced function of these receptors is correlated to the novel composition of NMDAR subunits due to alcohol exposure. In order to study the implications of alcohol compulsion and NMDARs, researchers must consider the ethical limitations of a clinical study model that would promote continued intake of alcohol in the face of negative consequences. Nonetheless, the nucleus accumbens of rodents is a known player in drug-motivated behavior. Past research has revealed active non-canonical NMDARs at hyperpolarized potentials within the nucleus accumbens of rodents play a critical role in compulsive-like alcohol behavior.[15,138] It has also been shown that inhibiting said NMDARs selectively reduces

compulsion-like alcohol drinking in rodents.[139] This data coincides with the limited research on humans that implicate NMDARs in alcohol craving with treatment-seeking subjects.[140] Ultimately, juxtaposing human and rodent studies reveal similarities of clinical pharmacological compounds that entail decreased ethanol consumption.[15]

Alcohol Withdrawal

Pertaining to the alcohol withdrawal and the effect it has on NMDARs, there seems to be a lasting effect of increased NMDAR expression/protein levels. The elevated function/activity of NMDARs observed can lead to high release of glutamate in the hippocampus leading to high Ca^{2+} concentrations.[141] Nonetheless, the impact NMDAR hyperexcitability may have on an individuals' physiological state correlates to epileptic seizures,[142] increased craving, and dysphoria.[143] With this in mind, we can evaluate the effects exercise has on NMDA subunit composition and function in the hippocampus and see if intervention is possible.

Exercise and NMDA Receptor Adaptations

When it comes to exercise, conflicting results are found for the NR2A and NR2B expression in the hippocampus. Voluntary wheel running has shown to increase NR2B expression in rodents, while resistance wheel running increases NR2A expression in the hippocampus of rats (Table 1). The study dedicated to evaluating high-intensity exercise on the NMDAR composition in Sprague-Dawley rats found initial elevated expression of both NR2A and NR2B subunits.[122] Although many studies may reveal conflicting results, it is evident to see the variation of subunit expression due to aerobic exercise (voluntary wheel running) versus anaerobic exercise (resistance training). These results can be compared to the use of pharmacological antagonists for the NR2B subunit to prevent the neurotoxic effect due to ethanol withdrawal. An NR2A antagonist was shown to prevent LTD in running mice but not in sedentary mice, showing an increase in involvement of the NR2A subunit of the hippocampus on neuronal plasticity.[19] Solomon and others found no change in subunit protein levels but did see a predominant increase in NR1 and NR2B hippocampal phosphorylation.[144] This phenomenon shows the capability of exercise altering protein kinase activity to impact receptor phosphorylation. We have provided examples in terms of NMDAR subunit contribution to LTP/LTD. This is not to say results are absolute, being that numerous studies contribute both NR2A and NR2B subunits to LTP and LTD.[145,146] Although there are studies done on receptor alterations due to exercise, most look into the impact it has on memory and recognition, which serves a benefit to research in LTP/LTD.

Implications for AUD Treatment

Recent research indicates that prediabetes, a condition characterized by impaired glucose regulation, may be analogous to reward dysregulation, the early stages of addiction.[147] To begin with, impaired central and peripheral insulin sensitivity, a hallmark of prediabetes, may contribute to worsened addiction, as the brain's reward pathways rely heavily on glucose and insulin signaling.[148] NMDAR in the limbic brain regions play a critical role in the emotional, behavioral, and clinical aspects of addiction[149,150] while abnormal insulin signaling affects NMDAR activity,[151,152] leading to changes in neurotransmission and further contributing to the development of addiction.[149,153,154] Furthermore, chronic alcohol use results in insulin resistance, exacerbating the negative effects of impaired glucose regulation on NMDAR signaling.[155–157] This may be reflected in the development of AUD and other addictive behaviors. Exercise has been proposed as a potential adjunctive therapy for addiction, including AUD.[158] Exercise is known to modulate NMDAR activity and sensitivity to alcohol, potentially mitigating the effects of impaired insulin signaling on addiction development. Further research is certainly needed to better define the heuristic value of exercise in the modulation of reward-linked receptors and addiction and its overall position within the therapeutic armamentarium for patients with addictive disorders.

Conclusion

Previous research has described the alterations of NMDARs in the cerebral cortex and hippocampus, this review prioritizes the hippocampus because of its pivotal role in memory formation and its direct ramifications for AUD. This paper outlined how NMDA receptors are influenced differently at various stages of ethanol use. Acute exposure generally inhibits NMDAR function, leading to neuroadaptive changes. Chronic exposure can cause an increase in

NMDA receptor subunit levels, altering synaptic transmission. During withdrawal, increased NMDAR expression may contribute to hyperexcitability. Exercise has shown promise in modulating these effects by influencing NMDA subunit composition and function, potentially mitigating the impact of ethanol use on NMDAR signaling. Compared to pharmacological studies, research on the impact of physical activity on these receptors is scarce. It is difficult to say which variation of physical activity (anaerobic versus aerobic) would lead to better outcomes of treatment if we solely evaluate subunit composition of NMDARs. Nonetheless, we know the activity of these receptors plays an important role in neuroplasticity and learning and memory, which of course are impacted by AUD. Based on the information highlighted in this review, aerobic exercise appears to have a more direct and comprehensive impact on the neurobiological, psychological, and physiological factors relevant to AUD and addiction recovery. This suggests a potential hypothesis that aerobic exercise could serve as an adjunct intervention technique for AUD treatment. Preclinical studies can explore not only the effects aerobic exercise has on NMDAR activity and modulation, but also what can be looked into in terms of these receptors and sensitivity to ethanol. Further research is warranted to fully assess the potential of exercise as a therapeutic intervention technique for AUD.

Funding

This research received no external funding.

Disclosure

Professor Kenneth Blum reports personal fees from VNI, Sunder Foundation, PEAKLOGIC, ADVANCED SPINECLINIC TUCSON AZ, ELECTRONIC WAVEFORM LABS; president of SYNAPATAMINE INC. The authors report no other conflicts of interest in this work.

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