

IMPACT



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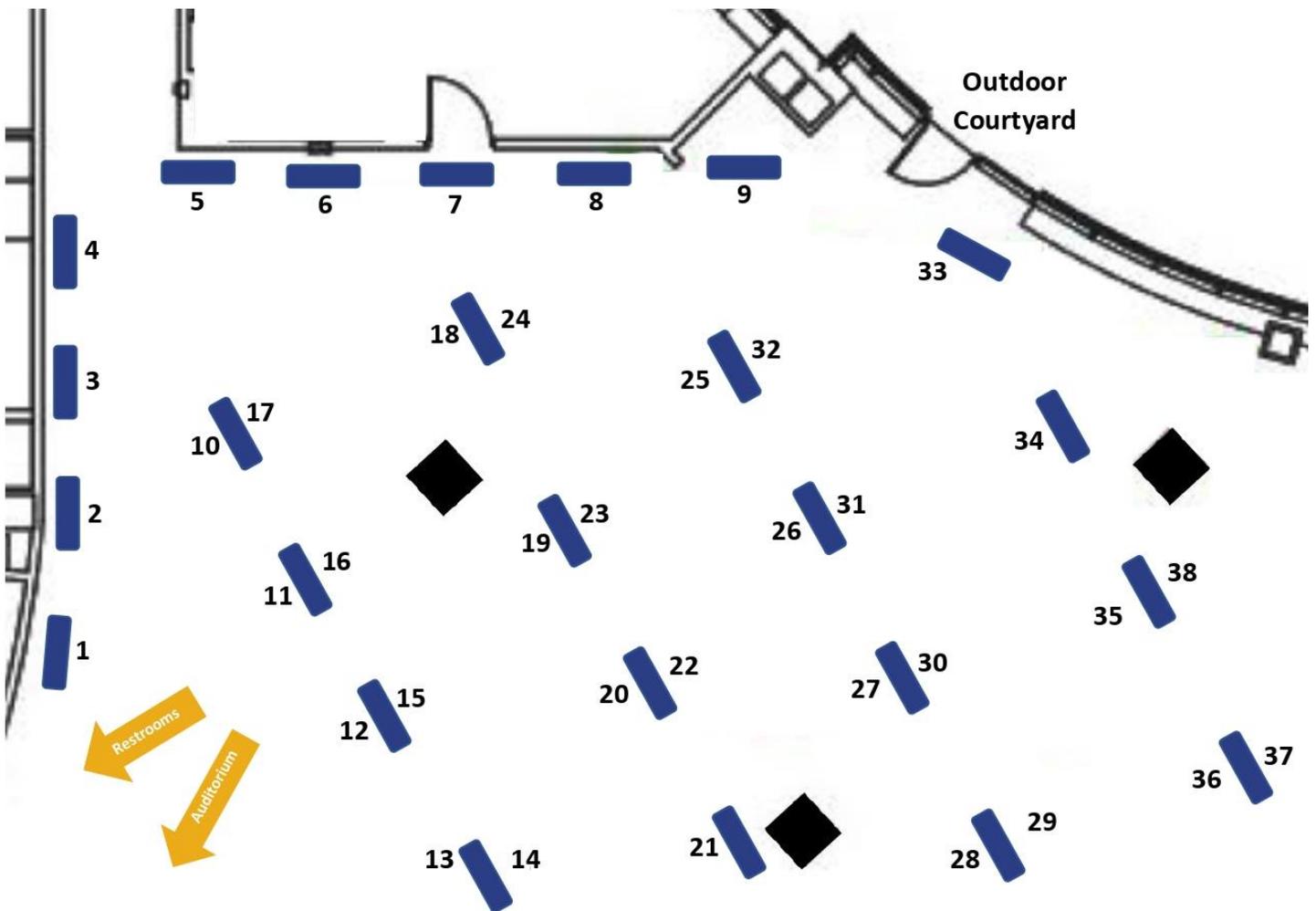
2020 IMPACT Symposium
March 7, 2020

Hypotheses & Abstracts

All posters will be displayed in the Atrium through lunch.

Poster Session 1 will take place from 9:30 to 10:15am. Teams with posters at odd-numbered locations will be delivering poster presentations at this time.

Poster Session 2 will take place from 10:20 to 11:05am. Teams with posters at even-numbered locations will be delivering poster presentations at this time.



Team’s hypotheses and abstracts are organized in this booklet by their poster location

Student Poster Presentations

1 Alcoholism and Probiotic Bacteria: Combatting Withdrawal Responses Using Probiotics

Abigail Alwin & Sophia Anderson

St. Olaf College // Faculty Sponsor: Laura Listenberger, Ph.D.

HYPOTHESIS: The activation of TLR4 initiates the inflammatory response, which contributes to withdrawal symptoms and an individual's ability to perform reversal learning. The use of probiotic bacteria may inhibit the activation of TLR4, thus preventing the addiction cycle.

The purpose of this research is to identify the mechanistic link between binge alcohol drinking, addiction, and the function of the neuroimmune system. Our hypothesis suggests that TLR4 initiates an inflammatory response following binge alcohol consumption. This inflammatory response produces the common symptoms associated with alcohol withdrawal, which we believe plays a significant role in inhibiting an individual's ability to perform reversal learning making an individual more susceptible to alcohol addiction¹. We propose that reinforcing and repairing gut epithelial membranes with a probiotic may prevent the activation of the TLR4 complexes that initiate the inflammatory response, thereby mitigating negative withdrawal symptoms and allowing individuals to perform reversal learning.

2 α -synuclein: The Link Between Binge Drinking, the Neuroimmune System, & Alcohol Addiction

Northwestern College // Faculty Advisor: Elizabeth Heeg, Ph.D.

HYPOTHESIS: An interesting area to investigate would be whether α -syn is the connecting factor between binge drinking, neuroimmune stimulation, and alcoholism. Specifically, we hypothesize that α -syn-activated microglia are toxic to hippocampal cells that are necessary for alcohol resistant behaviors (Figure 1).

Alcohol addiction is predominant around the world. Alcohol abuse can lead to a variety of degenerative cognitive functions, impaired emotions, and behavioral malfunctions (Ma and Zhu, 2014). There has been research linking neurotransmitters like dopamine, glutamate, opioid transmitters, norepinephrine, and many others to the behavioral and mental pathologies of alcohol addiction (Ma and Zhu, 2014). In this report, we hypothesize a mechanistic link between the alcohol-induced upregulation of α -synuclein(α -syn) in dopaminergic neurons to the cycle of alcohol addiction through microglial-mediated death of dopaminergic neurons. Understanding the molecular mechanistic links between binge drinking and alcohol addiction is crucial to comprehending resultant mental pathologies and can propose avenues for treatments.

3 Clock in Alcohol, Clock out Dopamine; Anomalies in Circadian Rhythm and Lymphatic System

Betra Alnaimat, Cierra Machado, Chidiogo Orakwue & Zamzam Shalle

University of Minnesota Rochester // Faculty Advisor: Rachel Olson, Ph.D.

HYPOTHESIS: We hypothesize that dysregulation of dopamine receptors due to anomalies in circadian clock gene expression and lymphatic circulation because of binge drinking results in an impaired neuroimmune system and subsequent addictive behavior.

4 Effects of Alcohol Induced Gut Dysbiosis and Leakage on the Neuroimmune System: Upregulation of Proinflammatory Cytokines Causes Neurodegeneration

Iya Abdulkarim, Talulah Mitchem, Hadia Mohammadzadah & Ken Wang

St. Olaf College // Faculty Advisor: Anne Walter, Ph.D.

HYPOTHESIS: We hypothesize that frequent alcohol use causes dysbiosis and gut leakage, triggering inflammatory responses that are communicated to the brain. Upregulation of proinflammatory cytokines such as TNF- α , IL-6, and IL-1 β aggravates neuroinflammation, resulting in depression and neurodegeneration in reward pathways leading to alcohol abuse. Thus, counteracting alcohol's effects on gut-initiated inflammation should lower alcohol abuse.

Alcohol is one of the most widely used and addictive substances. Once in the gut, alcohol induces dysbiosis and bacterial overgrowth. Increased permeability of the epithelial lining and LPS leakage trigger peripheral inflammatory responses. The Gut-Brain axis (GBA) communicates these responses into the brain, upregulating proinflammatory cytokines TNF- α , IL-6, and IL-1 β , resulting in

neuroinflammation. Chronic and frequent neuroinflammation can lead to progressive and selective destruction of dopaminergic neurons, which is linked to less pleasure, lack of impulse or control, anxiety and depression, and thus higher chance of alcohol dependency. Glucagon-like peptide 1 (GLP-1) is associated with food intake, anti-inflammatory responses, and reward pathways. We propose the use of GLP-1 analogs to attenuate neuroinflammation and activation of the mesolimbic pathway, reducing alcohol seeking behavior in humans.

5 Binge Drinking, Disrupted Circadian Rhythms, and Neuroinflammation: A Synergistic Pathway to Alcohol Use Disorder

Rebecca AbuAyed, Hannah Hwang, Stephanie Lum & Hassan Mian

Northwestern Health Sciences University // Faculty Advisors: Susan Lawrenz-Smith, Ph.D. and Lisa Oppedard, Ph.D.

HYPOTHESIS: Binge drinking and disrupted circadian rhythms increase gut permeability which leads to LPS-mediated neuroinflammation, dysregulating DAergic pathways and initiating the hypodopaminergic state that underpins the progression from binge drinking to addiction.

A body of biochemical data indicates that alcohol exposure leads to neuroimmune alterations. 1 Proinflammatory cytokines such as TNF- α and IL-6, as well as microglia and astrocytes, are primary activators of the neuroimmune system. 1,2 In addition to neuroinflammation, disrupted circadian rhythms and dopaminergic (DAergic) pathway abnormalities are also related to alcohol use disorder (AUD). 1,3 We propose a cyclic interaction between neuroinflammation, the DAergic system, and circadian rhythms in which binge drinking and disrupted circadian rhythms synergistically increase gut permeability, leading to LPS-mediated neuroinflammation. This disrupts DAergic pathways and leads to the hypodopaminergic state which facilitates the progression from binge drinking to addiction.

6 Neuroimmune System-Mediated Epigenetic Changes in Central Amygdala During Ethanol Withdrawal and Addiction Formation: The Role of Prolonged Neuroimmune System Signaling in Chromatin Deacetylation in the Context of Tolerance and Addiction Formation

Dominik Bakowski & Jaclyn Bracker

University of Wisconsin-Parkside // Faculty Advisor: Francis Mann, Ph.D.

HYPOTHESIS: We hypothesize that during the period of alcohol withdrawal, the ethanol-induced, prolonged generation of cytokines by neuroimmune cells in the central amygdala leads to a drastic increase of ROS production in the nearby neurons, which activate NF- κ B transcription factor leading to a subsequent upregulation of HDAC2 expression, and subsequent chromatin deacetylation. This outcome underlies a considerable decrease in dendritic spine density providing ground for diminished inhibitory GABAergic input to CeM neurons and thus deranged output to the brainstem—the underpinnings of anxiogenesis.

During binge drinking, a short-term ethanol-induced increase in chromatin acetylation in central amygdala neurons takes place, which underlies the proliferation of dendritic spines. This, combined with intensified GABAergic neurotransmission during intoxication, brings about anxiolytic effects. Importantly, alcohol also activates neuroimmune system cells via the TLR4 receptor, which initiates the production of cytokines and chemokines—the process that lasts long past ethanol metabolism. The excessive production of pro-inflammatory molecules indirectly contributes to a decrease of dendritic spine density as a result of enhanced histone deacetylases (HDACs) expression and lowered production of neurotrophic factors. These outcomes of neuroimmune system activation become drastic when ethanol is metabolized and no longer available to ensure blockage of HDACs or provide enhanced GABAergic neurotransmission. Ultimately, the CeM neurons send an abnormal output to the brain stem, which translates into anxiogenesis. The cumulative epigenetic effects, conditional learning, and negative reinforcement provide ground for tolerance, and ultimately addiction development.

7 Adolescent Alcohol Abuse: The Role of Neuroimmunity in the Cycle of Adolescent Addiction

Grace C. Cunningham, Michael J. Gregoria, Jackson L. Hammargren & Andy Y. Yang

Crown College // Faculty Advisor: Aeisha Thomas, Ph.D.

HYPOTHESIS: Binge alcohol drinking and addiction in adolescence compromises the neuroimmune system's role in development, specifically stalling the transition of control from the amygdala to the frontal lobes, which increases potential for a continuing loop of addiction.

Most adult alcohol abuse disorders (AUDs) begin in adolescence. Adolescent AUDs showcase the mechanistic link between the function of the neuroimmune system, addiction, and binge drinking. Many factors are tied both to adolescence and to addiction susceptibility. Our hypothesis suggests that AUDs in adolescence interfere with the process of neurodevelopment and perpetuate a cycle of alcohol abuse. Treatment suggested by our hypothesis can address symptoms and reduce risk of relapse.

8 The Effects of Ethanol on Microglia Activation and Neuroplasticity

Lily Courneya, Jessica Crosson, Jack Hackney & Savannah Martinson
University of Northwestern-St. Paul // Faculty Advisor: Gary Mumaugh, DC, FACO

HYPOTHESIS: We hypothesize that the metabolism of ethanol to acetaldehyde by ADH and catalase in the nucleus accumbens causes the release of free radicals, such as ROS. These species exhibit toxicity to nervous tissue, leading to neuronal cell death. The subsequent release of DAMPs, namely the nuclear protein HMGB1, partially activates microglia. This leads to the release of cytokines IL-1 β and TNF α , resulting in a loss of neuroplasticity in the neurons that function as the brain's reward system. This loss of neuroplasticity is accompanied by the onset of dependency on alcohol, as well as other substances that induce this physiological effect.

There have been suggestions that microglia play an important role in the activation of addiction. We proposed that the metabolism of ethanol affects levels of ROS and DAMPs, leading to the release of proinflammatory cytokines and a loss of neuroplasticity. The cytokines which have attributed to this effect are IL-1 β and TNF α . Further studies into this metabolic link may investigate drugs similar to fomepizole, which could prevent the metabolism of ethanol to its toxic product, acetaldehyde. This research may have a significant impact on those suffering from addiction around the world and may lead to a decrease in alcohol-associated incidents.

9 Can Theta Wave Induction Lower Inflammation and Alcohol Consumption in Mice?

Mackenzie Claypool, Emily Imm, Gabriella Lott & My Nguyen

College of Saint Benedict/Saint John's University // Faculty Advisor: Henry Jakubowski, Ph.D. and Edward McIntee, Ph.D.

HYPOTHESIS: Meditation, a non-pharmacological but well documented intervention that improves affective states, increases positive behavioral responses, and reduces alcohol consumption and binge drinking, works through increasing theta waves in brain areas central to affect and emotional regulation (ACC, amygdala, hippocampus). This leads to down-regulation of peripheral and central nervous system anti-inflammatory mediators, specifically TLR4 and its downstream signaling partners, which are upregulated by chronic and acute alcohol consumption.

Overconsumption of alcohol is one cause of chronic inflammation, which appears to be mediated by the canonical NF- κ B pathway. TLR4 (a pathogen and damage associated molecular pattern receptor) and HMGB1 (a nuclear DNA binding protein and damage associated pattern molecule) levels are elevated in postmortem brains of chronic alcoholics. Meditation has been found to be effective in treating excessive alcohol drinking as it elicits both psychological and biochemical effects through theta wave induction throughout the brain. We propose that meditation lowers expression of inflammatory markers in the brain and systemically, as well as elicits behavioral changes that lead to a decrease in ethanol consumption. We will mimic a meditative state using optogenetics to stimulate rhythmic theta waves in discrete areas of the brain. We will then measure changes in expression of molecules associated with the inflammatory state and correlate them with behavioral changes. The study of these interactions may provide potential new targets for therapeutic intervention.

10 TLR4: A target for Study of Alcohol induced Neuroinflammatory Responses and miRNA expression led by Alcohol addiction and Binge drinking

Ngim Chhamji Sherpa & Ritu Pandey

Minnesota State University Moorhead // Faculty Advisor: Adam Stocker, Ph.D.

HYPOTHESIS: We proposed that alcohol induces inflammatory signals through the activation of glial cells where TLR4 play a crucial role as TLR4 knockout prevents the neuroimmune response including the release of NF κ B, proinflammatory cytokines, and mediators and alteration of miRNA 200a/b expression.

TLR4 is associated with the expression of transcription factor NF- κ B, which regulates several cytokines involved in innate immunity [1]. The inflammatory responses are not evident in the TLR4 deficient mice suggesting that TLR4 plays an important role in the neuroimmune responses led by ethanol [2]. Ethanol treatment altered the expression of some miRNAs that targeted neuronal excitability but not in TLR4 KO mice [11]. Binge drinking was also found to be lowered the in TLR4 KO mice [4].

11 Effects of Alcohol on Estrogen Receptor β and the Neuroimmune System

Brooke DeSmith, Chase Caswell, Danielle Ertsgaard & Faith Malstrom

University of Northwestern-St. Paul // Faculty Advisor: Gary Mumaugh, DC, FACO

HYPOTHESIS: We hypothesize that there is a link between binge alcohol drinking, addiction, and the function of the neuroimmune system is that while estrogen has been associated with inhibition of the release of pro-inflammatory cytokines, there may be a malformation of estrogen receptor β (ER β) in the microglia which would prevent the proper processing of estrogen. This would cause an estrogen negative feedback loop that would increase the amount of estrogen being released but fail to inhibit the release of pro-inflammatory cytokines.

Due to the relationship between increased estrogen levels and pro-inflammatory cytokines in alcohol users, there may be a connection between estrogen receptor β (ER β) in microglia and alcohol consumption. This is significant because if there is a malformation in the ER β , this could lead to innovations in treatment for alcoholism. To research this idea further, a procedure such as a lumbar puncture could be used to test ER β after alcohol exposure for malformations.

12 Using miR-17 to Regulate TNF α Production During the Neuroimmune Response to Binge Alcoholism

Kathleen Edzards, Nick Marshall & Logan Spooner

Minnesota State University Moorhead // Faculty Advisor: Sumali Pandey, Ph.D.

HYPOTHESIS: TNF α and alcohol both cause changes in the activity of LGICs such as GABA α R, NMDAR (5)(7)(8)(16). TNF α indirectly causes chronic excitotoxicity in the CNS through TNFR1 signaling (5)(8)(11)(16). Ethanol and TNF α have disparate effects that play a role in alcohol addiction. In order to combat these changes, we propose that miR-17 is a novel, and testable candidate to down regulate the overproduction of TNF α through disruption of the autocrine loop which TNF α is regulated by.

Alcohol is one of the most used drugs in the world and current estimates state that one out of every six adults in the US binge drink at least once per week. Alcohol's effects on the brain cause an overall rise in inhibitory signaling that persist only for several hours, but how binge consumption of alcohol can lead to addictive behavior is still not well understood. Recent research has pointed to the activation of the innate immune system triggered by alcohol consumption as being a pivotal step in the development of binge alcohol addiction. Through a cascade of effects, ethanol triggers proinflammatory cytokine release in the CNS leading to chronic excitotoxicity which is detrimental to homeostatic function of the brain. It is thought that overproduction of TNF α during states of excitotoxicity could be disrupted by blocking its positive feedback loop. MicroRNA (miRNA) function as post-transcriptional modifiers that can enhance or block molecular pathways. Specifically, miRNA-17 in other diseases, such as Rheumatoid Arthritis, has been shown to downregulate the overproduction of TNF α during proinflammatory response. We propose that upregulation of the miRNA-17 could be a promising therapeutic approach to mediating the excitotoxic long-term effects that alcohol has on the brain. Returning the brain closer to basal levels of excitatory signaling will reduce the need for substances such as alcohol to combat excitotoxicity caused by the innate immune response.

13 Acute Inflammation in the VTA Coupled With Binge Drinking: The Mechanistic Link Triggering Chronic Neuroinflammation and Addiction

Stephen Engelhardt, Taylor Gordon, Madi Sundlof & Marie-Louise Tangu

Northwestern Health Sciences // Faculty Advisors: Susan Lawrenz-Smith, Ph.D. & Lisa Oppegard, Ph.D

HYPOTHESIS: Initial acute inflammation from a physical stressor, physiological stressor, mental illness, or injury, in the ventral tegmental area (VTA), coupled with binge ethanol drinking, creates an amplified inflammatory response. Ethanol use intensifies the initial increased and eventual decreased release of dopamine from dopaminergic neurons found in the VTA, signaling the rewarding effect. This cycle is mediated by the desensitization of GABA α 2-containing receptors and the increased expression of the proinflammatory cytokine TNF α , resulting in chronic neuroinflammation and triggering addiction.

Binge drinking results in a neuroinflammatory response, but inflammation can occur in the central nervous system (CNS), independent of ethanol exposure. This inflammation can be the result of a wide range of events, many of which are risk factors for alcohol use disorder (AUD). These can include depression, anxiety, infection, injury, or stressors, which result in a neuroinflammatory response, like that seen with ethanol consumption. This response promotes an increased release of the cytokine TNF α , which leads to a continuous, rapid release of dopaminergic signals. When dopamine is over-excited, it results in inflammation in the ventral tegmental area (VTA). Similarly, when ethanol is consumed, there is an increase in TNF α , the activation of microglia, and the desensitization of GABA α 2. When ethanol consumption and acute inflammation overlap, it results in an amplified response in the CNS, leading to chronic inflammation. If

binge drinking is repeated, this cycle leads to the habitual activation of the microglia cells and release of dopamine and TNF α , which diminishes the anti-inflammatory response. This over-production of TNF α also contributes to the amplified release of dopamine, which intensifies craving for ethanol, leading to addiction.

14 Kill Bili: How Elevated Bilirubin and Cytokine Levels Induce CNS Injury

Zachary Engel & Samantha Graber

University of Minnesota Rochester // Faculty Advisor: Rachel Olson, Ph.D.

HYPOTHESIS: HPA axis dysregulation and alterations in bilirubin levels and pro-inflammatory cytokines contribute toward CNS injury, subsequent addictive/ compulsive behavior, and neuroimmune impairment.

The hypothalamic-pituitary-adrenal (HPA) axis and bilirubin together increase pro-inflammatory cytokine production in splenic immune cells, microglia, and astrocytes. Bilirubin alters neuronal cell membranes, elevating intracellular calcium levels and impairs protein function ex: Calmodulin-dependent protein kinase II (CaMKII). Addictive behavior may be influenced by dysregulation of proteins CaMKII, calmodulin, and parvalbumin. Dysregulation of CaMKII desensitizes recombinant NMDA receptors so intracellular calcium levels may modulate synaptic plasticity and addictive behaviors.

15 CCL2 and Its Neuroprotective Effects: A Link Between Neuroinflammation and Alcoholism

Kaitlin K. Freese, Sydney Richetto & Kyla Stenzel

University of Wisconsin-Stevens Point // Faculty Advisor: Jennifer Bray, Ph.D.

HYPOTHESIS: The chemokine CCL2 provides a link between neuroinflammation and alcoholism due to its increased production upon ethanol exposure, ultimately providing a neuroprotective effect following subsequent ethanol use.

The chemokine CCL2 may play an important role in our understanding of how alcohol affects synaptic function. Studies show that CCL2 levels are upregulated with both acute and chronic ethanol use. The altered levels of CCL2 can dysregulate behavioral control systems that play a role in alcohol use disorders. Surprisingly, data suggests that CCL2 has neuroprotective properties against the effects of ethanol on synaptic plasticity by producing neuroadaptive changes in hippocampal neurons. Due to limited research on CCL2, further analysis should assess its role within the neuroimmune system as well as the consequences elevated levels of CCL2 have on central nervous system (CNS) function.

16 The Dynamic Glutamatergic System: A Mechanistic Link Between Binge Alcohol Drinking and the Function of the Neuroimmune System, and the Development and Maintenance of Alcohol Use Disorder

Zoe Garrett, Abby Grier, Maria Landherr & Burke Meader

St. Olaf College // Faculty Advisor: Shelly Dickinson, Ph.D.

HYPOTHESIS: Key changes to the glutamatergic system caused by patterned binge drinking include increased glutamate release by inflamed microglia, decreased astrocytic reuptake, and upregulation of NMDA receptors. This results in synaptic hyper-vulnerability to excitotoxic damage upon recurrent binge drinking events. Furthermore, increases in baseline glutamate release and NMDA receptor hypersensitivity are associated with the depressive effects of withdrawal in ethanol dependence. We hypothesize that these dynamic changes to the glutamatergic system are the mechanistic link between binge alcohol drinking, the neuroimmune system, and the development and progression of alcohol use disorder.

Glutamate is the most prevalent neurotransmitter in the brain with widespread functions and effects, including its role in the development of alcohol use disorder. Dynamic changes in the glutamatergic system - including decreased astrocytic reuptake, microglial hyperexpression of glutaminase, and NMDA-R upregulation - are key and relatively unexplored factors connecting binge alcohol drinking, neuroinflammation, and the development and progression of alcohol use disorder.

17 Connecting TLR-4, CN, NF-kB, and MMP in the Neuroinflammation and Alcohol Addiction Cycle

Betsy Holt, Molly Dirks & Ashley Jarvi

Crown College // Faculty Advisor: Aeisha Thomas, Ph.D.

HYPOTHESIS: Predisposing factors and the first exposure to alcohol both individually activate neuroimmune function, but together can cause enough neuroimmune stimulation to lead to binge drinking. This neuroimmune activation involves: (1) activation of calcineurin and TLR4=> NFkB=>MMP activation; (2) change of brain structure in the amygdala, and production of pro neuroinflammatory cytokines; (3) alcohol seeking; (4) binge drinking to addiction; (5) epigenetic changes in gene expression and the TLR-4 pathway; and finally (6) Increased inheritance and continuation of predisposing factors

Alcohol addiction and binge drinking are severe and prevalent conditions which induce a neuroimmune response. There are several neuroinflammatory conditions and genes that serve as predisposing factors. These predisposing factors in addition to alcohol drinking can lead to enough neuroinflammation to greatly increase the desire to drink and lead to binge drinking. Neuroinflammation leads to an increased desire to drink through activating toll-like-receptor-4 (TLR-4) and calcineurin (CN) pathways which activate the nuclear factor kappa-light-chain-enhancer (NF-kB) pathway leading to activation of matrix metalloproteinases (MMPs). Decreased dopamine production upon binge drinking is a key component to developing an alcohol addiction. Alcohol then induces epigenetic changes to promote neuroinflammation through remodeling of histone-4. This is novel in how it explains alcoholism as a cyclical process through neuroinflammation and connects the MMP, TLR-4, CN, through NF-kB.

18 Dual Effects of NFkB and LPS Endotoxin on the Neuroimmune System During Binge Alcohol Consumption: Finding the Mechanistic Link Between Addiction and the Neuroimmune System

Connor Holbrook, Hillary Kreager & Liane Mills

Northwestern Health Sciences University // Faculty Advisor: Susan Lawrenz-Smith, Ph.D.

HYPOTHESIS: The mechanistic link between binge alcohol drinking, addiction, and the function of the neuroimmune system is the activation of NFkB and how it alters the expression of certain non-inflammatory gene targets, such as opioid receptors and neuropeptides, and that these genes influence behaviors that can mediate addiction. NFkB is known to be part of the inflammatory pathway cascade activated by ethanol or drugs. NFkB also mediates complex behaviors including learning and memory, stress responses, and drug reward, which are processes that may lie outside the role of NFkB in the classic neuroimmune response.

Microglial activation when exposed to ethanol induces a hyper-ramified state. A hyper-ramified state causes swelling of the cell body, thickening of proximal processes, and reduction of distal ramification. Lipopolysaccharides (LPS) reside on the cell membrane of Gram-negative bacteria in the gut and disrupts permeability of the GI tract. Increased permeability allows for an influx of serum endotoxin levels in the blood stream. LPS stimulates inflammatory response of the neuroimmune system. The stimulated microglia then secrete cytokines. Pro-inflammatory cytokines receptors, such as TNF α , induce the release of NFkB. Protein-protein association networks, such as TLR-4 and TNF-R, play a role in downstream signaling resulting in NFkB regulation of gene expression in inflammatory responses, alcohol consumption, and addictive behaviors. We hypothesize that activation of NFkB mediates negative behavioral effects during alcohol and drug exposure, along with the known inflammatory response in the neuroimmune system activation. Research conducted on this hypothesis could lead to advancements in understanding the role of NFkB gene expression and pathways, as well as therapeutic solutions directly targeting NFkB.

19 MYD88 Signaling Inhibition: Interrupting TLR-4 Pathways to Close the Neuroimmune Positive Feedback Loop & Dopamine Stimulation

Katherine Hanna, RN; Keneisha McBean, LPN; Victor-Amrut Raikar; Vincent Mikaye, RN

Northwestern Health Sciences University // Faculty Advisors: Susan Lawrenz-Smith, Ph.D. & Lisa Opegard, Ph.D.

HYPOTHESIS: Interrupting the binding of MYD88 to TLR-4 during an instance of acute ethanol exposure would prevent the HMGB1/TLR-4 signaling pathway from progressing, and at the same time would reduce or eliminate IKK complex stimulation, which would prevent the release of dopamine

Binge drinking is described as the most common, costly, and deadliest pattern of excessive alcohol use in the United States, contributing to alcohol dependence and neurodegeneration⁵. It is associated with brain damage and addiction. However, the mechanistic link to the brain's neuroimmune system in regulating binge alcohol abuse and dependence may very well lie in the expression of the Toll-like receptor 4 (TLR-4). TLR4 has a direct relationship to MYD88 which signals and binds to TLR4. When the brain exposed to ethanol during and acute binge episode, there is an increase in inflammatory mediators like MYD88 and TLR-4 expression which in turn bind to one another on the cell surface and initiate an immune response to the presence of alcohol^{5,1}.

20 Dysbiosis of the Gut Microbiome may Explain a Mechanistic Link Between Binge Alcohol Drinking, Addiction, and the Function of the Neuroimmune System

Dania Johnson, Cyril Malle-Barlow, Grace Park & Alvin Sun

Northwestern Health Sciences University // Faculty Advisor: Susan Lawrenz-Smith, Ph.D & Lisa Opegard, Ph.D

HYPOTHESIS: Binge drinking induces changes in ratios of bacterial species in the gut microbiome which contributes to the development of leaky gut syndrome. This syndrome results in release of endotoxins into the bloodstream, initiating pro-inflammatory gene expression and ultimately a neuroinflammatory response. This inflammation cascade causes an increase in levels of neuroactive steroids and alters GABA receptor activity. In turn, the altered receptor activity leads to dysregulation of the reward pathway which potentiates alcohol addiction.

Alcohol consumption causes alterations in the gut microbiome composition by decreasing Faecalibacterium prausnitzii and increasing Proteobacteria. This can lead to increased permeability of the intestinal lining which allows LPS to be secreted into systemic circulation. As a result, a neuroinflammatory response is initiated by pro-inflammatory cytokines and amplified by transcription factor NF- κ B. The heightened neuroinflammation leads to increased levels of the neuroactive steroid dehydroepiandrosterone which inhibits GABA-A receptor activity. This disrupts the normal function of the mesolimbic pathway intensifying alcohol addiction.

21 The Effect of Alcoholism on LPS and Mesolimbic Neurotransmitter Metabolites via the TNF- α Proinflammatory Pathway: Investigating the Changes in Metabolites of the Mesolimbic Pathway in Relation to LPS and TNF-A Levels As a Result of Increased Alcohol Intake and Addiction

Luzan JadKarim & Kayden Dangremond

Coe College // Faculty Advisor: Cassy Cozine, Ph.D.

HYPOTHESIS: Alcoholism leads to increased LPS permeability in the liver and bloodstream, leading to heightened TNF- α levels and therefore heightened serotonin metabolites (5-HIAA) and heightened dopamine metabolites (HVA) in the nucleus accumbens, promoting addiction via the mesolimbic pathway.

Alcohol is a general nervous system depressant and is known to impact various neurotransmitters in inhibitory and excitatory pathways. Studies have shown that increased alcohol intake leads to increased endotoxin levels in the blood and neuroinflammation

22 An Inflammatory Bowel Disease: Chronic Inflammation of the Gut due to Alcohol Consumption

Howard Leuschen, Cyrus Nourae, Dylan Ross & Kassra Taghizadeh

University of Minnesota-Twin Cities // Faculty Advisor: Ben Saunders, Ph.D.

HYPOTHESIS: We hypothesized that with a decrease in gut inflammation and permeability, there will be a decrease in neural activation of addiction pathways.

Binge drinking is a phenomena that negatively impacts many people. There are many similarities between inflammatory bowel diseases (IBDs) and chronic alcohol consumption (CAC) (gut inflammation, thinning of mucosal lining of gut, increased gut permeability). CAC leads to inflammation that can impact the nervous system and lead to addiction. Due to the similarities between IBDs and CAC, we are proposing that CAC is an IBD: with a decrease in gut inflammation and permeability, there will be a decrease in neural activation of addiction pathways. IBD treatments (Infliximab, steroids, or other immunosuppressants) can be investigated in the treatment of CAC.

23 Δ FosB Isoforms alter Cdk5 Expression Linking the Neuroinflammatory Response and Addictive Behaviors: Alteration of CDK5 Expression Increases Synaptic Activity Leading to Dendritic Thickening

Cattera Leavens, Allie Easker & Katrina Barnes

University of Wisconsin-Eau Claire // Faculty Advisor: Jamie Lyman Gingerich, Ph.D.

HYPOTHESIS: Binge-alcohol drinking triggers a neuroimmune response through TLR4, which results in chromatin remodeling and expression. This leads to Δ FosB expression and isoform accumulation. Δ FosB isoforms upregulate Cdk5 expression, sensitizing processes involved in alcohol addiction.

Binge-alcohol drinking triggers a neuroimmune response which results in chromatin remodeling and expression. We propose that this leads to the alteration of fosb and upregulation of Cdk5, sensitizing processes involved in alcohol addiction. Through a series of mechanisms involving HMGB1 and TLR4, histone 4 is acetylated, which allows for preferential expression of transcription factors, specifically, Δ FosB. Δ FosB isoforms accumulate after alcohol exposure due to its high stability and half life. When Δ FosB isoforms bind to AP-1 sites on neurons, Cdk5 is upregulated, increasing synaptic activity in the limbic region of the brain. To compensate for the overstimulation, dendritic spines thicken. This dendritic spine thickening makes the brain more sensitive to subsequent alcohol exposure and addiction

24 The Roles of IL-6 and IL-10 in the Neuroimmune Response to Binge Drinking and Addiction

Alyssa Miller, Ashton Miller, Bailey Van Eyll & Brenda Thao

Northwestern Health Sciences University // Faculty Advisor: Susan Lawrenz-Smith, Ph.D.

HYPOTHESIS: We hypothesize that when a human body is exposed to foreign substances such as alcohol, it is common for inflammation to occur. In the case of binge drinking, pro-inflammatory cytokine IL-6 is released by the body to preserve cell function and prevent cell death. Due to alcohol causing CNS depression, anti-inflammatory cytokines such as IL-10 cannot be released to decrease the inflammation. Once the alcohol is metabolized and eliminated from the body there is a surge of IL-10 that causes new alcohol cravings due to withdrawal symptoms. This causes further alcohol consumption creating a cytokine feedback loop of pro and anti inflammatory cytokines.

When alcohol is consumed, the innate immune system responds by releasing a pro-inflammatory cytokine such as Interleukin 6 (IL-6) to attack the foreign substance. It concurrently attempts to inhibit cell death caused by ethanol by releasing anti-inflammatory cytokines such as Interleukin 10 (IL-10).¹⁰The innate immune system involved are ultimately controlled by the body's central nervous system. When the brain is intoxicated by alcohol, the central nervous system is inhibited resulting in a decreased anti-inflammatory response leading to the acute pro-inflammatory response not returning to baseline and becoming a chronic problem.

25 Localized HMGB1 from repeated binge alcohol episodes induces cyclical cytokine-cascades increasing likelihood of addiction

Cam Mackay, Nick Moore, Kayla Morissette & Danny Santana

Northwestern Health Sciences University // Faculty Advisors: Susan Lawrenz-Smith, Ph.D. & Lisa Oppegard, Ph.D.

HYPOTHESIS: Repeated binge alcohol events trigger increased levels of HMGB1, TNF- α , and IL-1 β , which causes neural cell death, a loss of executive functioning in the prefrontal cortex, and increased alcoholic cravings leading to addiction

Ethanol is absorbed by the gut and will cross the blood brain barrier. Microglial cells exposed to ethanol may trigger an innate immune response by releasing proteins into the extracellular space. HMGB1 activates TLR-4 and RAGE pathway receptors that increase production of these cytokines. Repeated cycles of binge alcohol consumption can up regulate receptor expression and lead to stronger immune responses. Immune responses have the potential to damage nearby neural cells which can lead to cell death. The loss of neurons will reduce executive functioning, impulse control and may contribute to addiction behavior. To prevent this development, we propose a drug-intervention therapy that cleaves extracellular HMGB1 to prevent the inappropriate activation of these pathways.

26 Pro-inflammatory Cytokine Interleukin-1beta (IL-1 β) Activates Alcoholism Cycle: With Approaches from the Kynurenine Pathway and Suppressing NLRP-3 to Abolish Alcohol Addiction

Duong Nguyen & Sofia Perez

Concordia College // Faculty Advisor: Krys Strand, Ph.D.

HYPOTHESIS: Alcohol intake can sensitize the neuroimmune system, persistently increasing the level of IL-1 β and maintaining the depressive stage in alcohol consumers. Moreover, alcohol also causes a short-term boost of the reward pathway by releasing dopamine in the brain contributing to the repeating binge consumption of alcohol.

Up to 2018, about 90,000 alcohol-related deaths in the U.S. were recorded annually¹. Therefore, exploring the mechanistic link to binge alcohol consumption behavior is crucial to reduce death rates. Pro-inflammatory cytokine Interleukin-1beta (IL-1 β), released from ethanol intake, is the key factor that causes depressive stage on consumers. Simultaneously, ethanol also generates the reward pathway by increasing in dopamine². These processes create a vicious cycle of alcoholism. Furthermore, we propose two treatments to

alcohol consumers: 1) the use of oral consumption of JM6 and Ro61-8084 to inhibit the expression of kynurenine, and 2) Danggui Buxue Tang (DBT) to suppress NLRP-3 inflammasome. This will result in a better understanding of the mechanistic link and provide direction for future research.

27 Role of Intestinal Microbiota in Alcohol Addiction and the Link to the Neuroimmune system

Melanie Nuthals, Joseph Manual, Perkell Collie & Kiahltone Thao

Northwestern Health Sciences University // Faculty Advisors: Susan Lawrenz-Smith, Ph.D & Lisa Oppeward, Ph.D

HYPOTHESIS: The link between binge alcohol drinking, addiction, and the neuroimmune system is through the intestinal microbiota and its responses to alcohol exposure.

Nationally, alcohol use is the third leading preventable cause of death¹. With increased alcohol consumption, there is an increase in inflammatory response. In turn this can lead to increased intestinal permeability. Levels of IL-1B inflammasome markers in the hippocampus rise with excess alcohol use, leading to neurodegeneration and addiction. The evaluation of the intestinal microbiota could provide insight to potential links between alcohol addiction and the neuroimmune system.

28 Activation of IL6 Through TLR4 Signaling: Pro-Inflammatory Signals Promote Addictive Behaviors

Sabrina Nagy, Sabah Sulaiman, Jordan Villa & Watfae Zayed

DePaul University // Faculty Advisor: Sean Austin Lim, Ph.D.

HYPOTHESIS: SNPs in the GABAA α 2 subunit change the signaling of TLR4 receptors which trigger a neuroinflammatory response through IL-6 in alcohol addiction behaviors across individuals.

In considering the disease of alcohol addiction, SNPs in the GABAA α 2 subunit change the signaling of TLR4 receptors which trigger a neuroinflammatory response through IL-6 in alcohol addiction behaviors across individuals based on the MYD88 signaling pathways.

29 Vagus Stimulation By Alcohol Leads to Addiction: The Relationship Between the Neuroimmune System and Afferent Vagus Nerve Signals

Anna G Przybelski, Aspen Gunnlaugsson & Rebekah Kolenda

Ripon College // Faculty Advisor: Babara Sisson, Ph.D.

HYPOTHESIS: Alcohol stimulating the vagus nerve in the upper gastrointestinal system has an immediate and profound effect on the neuroimmune system, initiating the clinical cascade resulting in intoxication and ultimately addiction.

The affects of alcohol on the human body is thought to reach the blood brain barrier by way of the bloodstream after it is absorbed by mucosal membranes in the small intestine. Our hypothesis and proposed experimental design analyzes the possibility of the afferent vagus nerve signals being the leading member in the relationship between the neuroimmune system and addiction.

30 Can We Be Immune to the Cycle?: The Role of TLR4 in CS-Reinstatement of Ethanol Administration

Bethany Saxon, Nathan Popodi, Anna Brodjian & Sara Klimisch

University of Wisconsin-Whitewater // Faculty Advisor: Matthew Andrzejewski, Ph.D.

HYPOTHESIS: What is the role of the inflammation initiating TLR4 in alcohol cravings in young rats?

In their review "The Role of Neuroimmune Signaling in Alcoholism," Crews et. al. emphasize that neuroinflammation plays a critical, and surprising, role in alcohol abuse via well-known inflammatory mechanisms. Using their model as a guide, our study proposes to explore the specific role of Toll-Like receptor 4 (TLR4) in neuroinflammation. If our study proves successful, the administration of resatorvid -TAK 242 - may help prevent alcohol cravings.

31 MCP-1 & Microglia Upregulation in AUD

Sydney Schwitters, Maison Bry, Caleb Johnston & Guerin Szafraniec
University of Northwestern–St. Paul // Faculty Advisor: Gary Mumaugh, DC, FACO

HYPOTHESIS: We hypothesize that an upregulation of microglial cells during the withdrawal phase after alcohol consumption will cause a subsequent increase in Monocyte Chemoattractant Protein-1 (MCP-1) which is a proinflammatory cytokine.

Our research investigates the effects of alcohol on the neuroimmune system. Our hypothesis explains that the microglia and MCP-1 cycle increases the desire for alcohol consumption and leads to addiction. If this cycle is broken, the urge to consume alcohol may decrease significantly among people suffering from Alcohol Use Disorder (AUD) and binge drinking. This could possibly be accomplished through exosomes, containing curcumin, introduced intranasally which may decrease microglial counts within the brain.

32 TGF- β INHIBITION OF IL-1 β ACTIVITY IN ACUTE BINGE ALCOHOL CONSUMPTION: Anti-Inflammatory Treatment for Withdrawal Symptoms

Sara Saintil, Shealuck Vang, Katrina Sewell & Polycarpe Bagereka
Carleton College // Faculty Advisor: Debby Walser-Kuntz, Ph.D.

HYPOTHESIS: Literature supports that pro-inflammatory IL-1(beta) is involved in the activation of withdrawal symptoms within the brain after acute alcohol consumption. We hypothesize that TGF-(beta), an immunosuppressive cytokine, will interrupt the pro-inflammatory response observed 6 to 18 hours after acute binge drinking.

Acute binge drinking has been shown to have adverse health effects on brain function following alcohol consumption. Significant pro-inflammatory immune molecules, such as IL-1 (beta), are activated and initiate a proinflammatory neuroimmune response followed by withdrawal symptoms. Literature supports that the short time period (approximately 12 hours) between the pro-inflammatory response and the initiation of withdrawal symptoms, introduces a window where anti-inflammatory functioning cytokines, such as TGF-(beta), can intervene. Our hypothesis suggests that the introduction of TGF-(beta) to the brain prior to the pro-inflammatory response of IL-1(beta), can prevent withdrawal symptoms and reduce acute binge alcohol neurodegeneration.

33 LPS Upregulates Pro-inflammatory Cytokine Production via TLR2-TLR4-CD14 Receptor Complex Signaling

Zachary Strickland, Kenneth David & Ingrid Jacobson
Concordia College // Faculty Advisor: Julie Mach, Ph.D.

HYPOTHESIS: Binge drinking damages intestinal integrity and elevates levels of the bacterial endotoxin lipopolysaccharide (LPS). LPS bind to the receptor complex TLR2-TLR4-CD14, located at the blood-brain barrier, which activates the transcription factor NF-kB. NF-kB upregulates pro-inflammatory cytokines that activate microglia. Continued activation of these microglia damage the pre-frontal cortex (PFC) and the mesolimbic dopaminergic reward system. Disrupted PFC and reward system activity contributes to weakened decision-making, craving, and compulsive alcohol use—hallmarks of addiction.

Alcohol Use Disorder (AUD), the most common substance abuse disorder in the United States, is linked to binge drinking behaviors. Binge drinking activates the neuroimmune system via pro-inflammatory cytokine release. Chronic binge drinking causes chronic neuroinflammation, which leads to symptoms of AUD. The mechanistic link between binge drinking and AUD currently remains unknown. Our research suggests that the TLR2-TLR4-CD14 receptor complex plays a novel role linking Binge-alcohol drinking, alcohol use disorders, and the neuro-immune system through Lipopolysaccharide (LPS) activation

34 TLR4 Activation Promotes Addictive Binge Alcohol Drinking Through Multiple Positive Feedback Loops

Alissa VanDenBoom & Robert VanDenBoom
Century College // faculty advisor: Michelle LeBeau, Ph.D.

HYPOTHESIS: Stress and alcohol use induces the TLR4 signaling pathway and promotes persistent and progressive activation of the neuroimmune system via cytokines and transcription factor AP-1, leading to alcohol-associated addictive behaviors. This positive feedback loop by way of the TLR4 receptor is the mechanism which links binge alcohol drinking, addiction and the neuroimmune system.

Alcoholism is a common substance use disorder. Binge drinking, a subtype of alcoholism, is an addictive behavior and results in the activation of the neuroimmune system. Stress and alcohol result in systematic release of LPS and HMGB1, both of which activate the TLR4 receptor protein. Activation of the TLR4 receptor protein results in a release of NF- κ B and AP-1. NF- κ B release modulates the transcription of pro-inflammatory cytokines TNF α , IL-1 β , IL-6 and IL-8, all of which are correlated with alcohol severity and have been implicated in behavioral responses associated with alcoholism. AP-1 is a transcription factor for an enhancer region for the TLR4 gene. We hypothesize that the induction of the TLR4 pathway by either stress or alcohol promotes the progressive and persistent activation of the neuroimmune system via the transcription factor AP-1 and pro-inflammatory cytokines. Increases in NF- κ B induced pro-inflammatory cytokines promotes addictive behaviors while increases in AP-1 result in sensitization of the neuroimmune system. The activation of TLR4 is a positive feedback loop which links binge alcohol drinking, addiction and the neuroimmune system. Blocking the TLR4 receptor with an antagonist, naltrexone, is a current treatment for alcoholism; however, naltrexone by itself is not sufficient to treat alcoholism, suggesting that further research utilizing other known TLR4 antagonists is necessary.

35 Neuroimmune Mechanisms of Alcohol Addiction

Kylie VanDyke, Xuyang Zhaoxin & MeilinTang

University of Wisconsin-Eau Claire—Barron County // Faculty Advisor: Wufeng Tian, Ph.D.

HYPOTHESIS: The brain is altered during times of intoxication and is manipulated in terms of cytokines and neurotransmitters so that the individual must drink alcohol in order to normalize their brain's behaviors. Preexisting differences in GABAergic gene expression in the CeA may also influence susceptibility to developing alcohol addiction.

In this poster, we reviewed the persisting cause of alcoholism and proposed the idea that the main links between binge drinking and the function of the neuroimmune involved the manipulation of cytokines and neurotransmitters. The studies and experiments indicted that there are relations in the cytokine levels of those who are intoxicated and how a certain percentage (15%) of the population is predisposed to be addicted to alcohol. We believe that alcoholism is linked with the changed neurochemistry due to alcohol exposure; the cytokine levels were altered, genes manipulated, and gray matter destroyed during long term abuse of alcohol. Treatments could take advantage of the relationship between alcohol and the neuroimmune system to subdue the "excessive consumption" of individuals and end alcohol's manipulation of cytokine concentrations, neurotransmitters' ireregulation, and rebalance the brain.

36 The impact of binge drinking patterns on NF- κ B expression in Wister rats: Comparing Daily Drinking to Drinking Three Days a Week

Danielle Veese, Eyram Agbenya, Mindy Glaser & Kadeesha Duncan

Marian University // Faculty Advisors: Sheryl Ayala, Ed.D.; Jon Nicoud, Ph.D. & Amy Hennings, Ph.D.

HYPOTHESIS: Male Wister rats given three g/kg of 20% (w/v) ethanol every day versus cycles of the same dosage for three days and then four days without will have different levels of NF- κ B expression in the prefrontal cortex associated with different levels of addictive behavior.

At issue is the possible differential effect of intermittent binge versus chronic binge drinking. This study tests the expression of NF- κ B in male Wister rats following exposure to binge alcohol levels (three g/kg) daily and a schedule of three days with ethanol and four days without for 28 days. The three days on and four days off models social binge drinking. NF- κ B is a causative agent in inflammation which plays a role in addiction (Crews, et al., 2017). By understanding the NF- κ B expression following social binge drinking it is possible to gain insight into the implications of heavy drinking on the weekends and routine college partying.

37 The Influence of Interleukin-6 in Addiction, Binge Alcohol Drinking, and the Neuroimmune System

Elizabeth Valine, Jennifer Bowman, Alycia Abler & Antonia Fritz

University of Northwestern-St. Paul // Faculty Advisor: Gary Mumaugh, DC, FACO

HYPOTHESIS: We hypothesize that interleukin-6, which is heightened during ethanol consumption, causes the downregulation of serotonin transporter (SERT) by inducing the phosphorylation and translocation of Signal Transducer and Activator of Transcription 3 (STAT-3) into the nucleus to suppress SERT expression [7]. We propose that decreased SERT activity leads to an elevation of 5-HT in the synaptic cleft, which interacts with 5-HT receptors including 5-HT1A, 5-HT1B, 5-HT2 5-HT3, associated with increased consummatory behavior, rewarding effects, and intoxicating effects of alcohol. Additionally, 5-HT has been linked to decreased reuptake DA [10].

Our research investigates the down-regulation of serotonin transporter (SERT) via the induction interleukin-6 (IL-6), a pro-inflammatory cytokine involved in neuroimmune responses, in conjunction with Signal Transducer and Activator of Transcription 3 (STAT-3). We propose that decreased SERT activity leads to elevated serotonin (5-HT) in the synaptic cleft, which interacts with serotonin receptors including 5-HT1A, 5-HT1B, 5-HT2 5-HT3, associated with the increased consummatory behavior, rewarding effects, intoxicating effects, and withdrawal anxiety characteristic of alcohol addiction.

38 Binge Drinking Causes Neuroimmune Activation and Dysregulation of Ghrelin Receptor Heteromers in the VTA Modulating Addictive Behaviors

Nick VanRaden, Andrea Schaefer, Asma Mohammed & Kayla Mehrer
Minnesota State University Moorhead // Faculty Advisors: Adam Stocker, Ph.D.

HYPOTHESIS: Binge alcohol consumption causes systemic inflammation and disruption of ghrelin signaling, followed by chronic maladaptive neuroimmune signaling that modulates GHS-R1a:DRD2 heteromer formation in the VTA, resulting in aberrant dopamine signaling in the mesolimbic pathway, leading to addictive behaviors.

Neuroinflammation can result from systemic inflammation caused by binge alcohol drinking and/or addiction. However, the underlying mechanisms behind how neuroinflammation modulates addictive behaviors remains largely inconclusive. Ghrelin, also known as the hunger hormone, has been found to increase addictive behaviors while also having anti-inflammatory effects and is altered by alcohol consumption. Ghrelin's receptor, GHS-R1a, has also been shown to form a heteromeric complex in hypothalamic neurons that co-express dopaminergic D2 receptors (DRD2). Research has demonstrated that the formation of a DRD2:GHS-R1a heteromer is required for the anorexic murine behavior, and blockade or KO of the GHS-R1a prevented DRD2 agonism by dopamine in that region and prevented anorexia. Furthermore, GHS-R1a is expressed in more than 50% of dopaminergic Ventral Tegmental Area (VTA) neurons—a highly heterogenous brain region in the mesolimbic pathway which is known for reward and motivation behaviors. Therefore, we propose binge alcohol consumption causes systemic inflammation and disruption of ghrelin signaling, followed by chronic maladaptive neuroimmune signaling that modulates GHS-R1a:DRD2 heteromer formation in the VTA resulting in aberrant dopamine signaling in the mesolimbic pathway leading to addictive behaviors.