The Links Between Stress, Signalling and Excessive Alcohol Consumption

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Scientia

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While alcohol is often consumed to help us relieve stress and relax, excessive consumption can negatively impact the way that our brains process and cope with stress, leading to further difficulties. **Dr Lara Hwa** from the Department of Psychology and Neuroscience at Baylor University is investigating the link between external stressors and stress signalling in the brain to understand how these processes govern excessive drinking.

The Link Between Alcohol and Stress

Alcohol abuse has a tremendous toll on society, with impacts ranging from increased healthcare costs and crime to losses in workplace productivity. With respect to healthcare, long-term drinking has been shown to have several detrimental effects on our health, including negatively affecting systems in our brain that help us to process and cope with stress. Alcohol consumption and stress have long been linked and it is thought that we drink alcohol to relieve stress and relax. Yet, despite this long-held theory, we still do not fully understand the link between the nervous system and this behaviour.

Stress has been shown to drive social drinking. It can also be responsible for relapse in people with alcohol use disorders. Chronic alcohol drinking also causes stress by impacting the stress systems in the brain which can, in turn, govern excessive drinking. One theory is that the progression from high alcohol intake to alcohol dependence may be driven by repeated cycles of heavy drinking followed by deprivation. This area of research is particularly important for understanding the link between psychological mechanisms and the underlying neurobiology of relapse behaviour. By understanding this link, researchers may be able to identify therapeutic targets that will improve the treatment of addiction.

Dr Lara Hwa at Baylor University uses a variety of experimental techniques to investigate how external stressors and endogenous stress signalling in the brain govern excessive drinking. This important research is elucidating how stress and the availability of alcohol interact with brain mechanisms, and will help us to design better treatment plans for alcohol use disorders.

Episodic Drinking Increases Alcohol Consumption

Excessive alcohol use and binge drinking have been shown to cause an increased risk for a variety of health problems including injuries, violence, liver diseases and cancer. As such, research has focused on the links between binge drinking and increased alcohol consumption. Previous research has shown that intermittent, or limited, access to alcohol ultimately leads to an increase in consumption.

In a study published in 2011, Dr Hwa and her colleagues explored escalated drinking behaviour in adult C57BL/6J mice given intermittent access to alcohol. C57BL/6J mice are a laboratory strain of mice that are widely used in research as models of human disease. These mice also exhibit high alcohol intake compared to other strains, making them conceivable models on which to examine how intermittent access to alcohol can affect alcohol consumption. Dr Hwa found that mice that were given intermittent access to alcohol drank more in a two-hour 'binge' period and across the 24-hour day than those that were given consistent, continuous access to alcohol, even when fresh water was available.

In addition to looking at intermittent access, another avenue that has been explored is the alcohol deprivation

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effect, whereby periods of alcohol access are alternated with periods of deprivation in weekly cycles. Dr Hwa showed that some mice that were given intermittent access to alcohol demonstrated symptoms of withdrawal, indicating a potential parallel to the withdrawal symptoms suffered by human patients with alcoholism.

Reducing Intermittent Alcohol Consumption

As research in this area develops, several pharmacotherapies have been explored that aim to target specific areas of the brain to reduce intermittent alcohol drinking. For example, naltrexone is an opioid antagonist that works to block opioids from binding to receptors in the brain. This drug has also been shown to reduce alcohol drinking both during intermittent and continuous access by up to 20%.

The discovery of compounds like naltrexone and the identification of their beneficial effects suggest that certain receptors in the brain play a role in excessive alcohol consumption and that these receptors are good targets for therapeutic interventions. In addition, it has been shown that using a combination of these therapies could be useful in further reducing intermittent alcohol drinking.

Dr Hwa built on this previous research to investigate the use of two such therapeutic interventions, naltrexone and a corticotropin-releasing factor type-1 receptor (CRF-R1) antagonist, to see if they act independently or dependently in a certain area of the brain known as the dorsal raphe nucleus to reduce intermittent alcohol drinking in mice. The results demonstrated that both therapeutic interventions reduced intermittent alcohol consumption in mice when administered independently and when given together. However, the two compounds did not additively suppress alcohol drinking, suggesting that both act via a common mechanism in reducing alcohol intake.

The CRF-R1 is a binding site for corticotropin-releasing factor (CRF) which is a neuropeptide involved in the endocrine stress response within the body. CRF initiates this stress response which results in a whole suite of reactions that lead to an increase in stress hormones, such as corticosterone which help to combat stress through initiating several changes within the body. Not only has CRF been shown to be involved in the stress response, but it has also been linked to heavy alcohol drinking. Previous studies have demonstrated that social defeat and subordination stress in mice and monkeys can lead to increased alcohol consumption when compared to non-stressed or more highly ranking individuals.

In a second study also published in 2016, Dr Hwa and colleagues investigated the link between social stress and increased alcohol consumption. This study explored the mechanistic link between social stress and drinking and the role that CRF receptors – namely CRF-R1 – play in this relationship, again using mice as a model.

The researchers demonstrated that stress increased voluntary alcohol drinking in mice that had a history of social defeat. Social defeat is a type of social stress that is chronic and is characterised by hostile interactions. This type of stress is identifiable in both humans and animals, and is capable of causing significant changes in behaviour, brain functioning, neurotransmitter and hormone levels

as well as health. In this study, mice that experienced brief episodes of defeat stress for ten days consumed more alcohol and preferred more alcohol than non-stressed mice.

The research team also showed that treating mice with a CRF-R1 antagonist which blocked CRF from binding to its receptor was an effective treatment for reducing alcohol intake in both stressed and non-stressed mice that were given intermittent access to alcohol. Interestingly, this treatment did not reduce intake in mice given continuous access to alcohol. Together, these results show that both intermittent alcohol availability and the stress experienced can influence the brain stress systems. CRF-R1 may be a neural target that becomes adapted in long-term heavy drinkers, but not as much in social drinkers. Thus, these experiments and others imply that administering a CRF-R1 antagonist may be a viable treatment to help balance the dysregulation of stress and reward in alcohol use disorders.

Long-term Links Between Alcohol and Stress

The next step in looking at the link between alcohol consumption and stress signalling is to understand how drinking alcohol impacts the ability of the brain to cope with stress in the long term. Maladaptive responses to stress have long been associated with alcohol consumption and are the hallmark of alcohol use disorders. Alcohol has been shown to alter the hormonal balance as well as the way the body perceives and responds to stress but only limited research has looked at the underlying mechanisms behind this.

The neuropeptide prodynorphin (Pdyn) and its receptor is a molecule that is linked to another stress system that operates in the brain which has been studied with relation to mood and alcohol disorders. To look at the link between alcohol and abnormal stress responses, a recent study by Dr Hwa published in 2020 explored whether stress signalling in the brain linked to Pdyn regulates altered stress responses after long-term alcohol drinking. To do this, the researchers used mice that had been subjected to six weeks of intermittent alcohol access and exposed them to a stressor, which in this case was the scent of a predator, an odour isolated from fox faeces.

The results demonstrated that the signalling initiated by Pdyn and its receptor in the brain disrupts stress-related behavioural responses following heavy alcohol drinking. It appears that this is because stressed mice with a history of alcohol drinking had increased activity in a part of their brain known as the corticolimbic system, specifically from the prefrontal cortex to the bed nucleus of the stria terminalis. This system, among others, is responsible for processing a broad range of behavioural and cognitive functions, including decision-making and emotional regulation.

These important results provide further insight into the links between these systems in the brain and how neuropeptide signalling can be altered by stress and alcohol consumption. As Dr Hwa explains, 'The connection between stress and alcohol use is highly complex. On one hand, there is the idea of having a drink to "steady the nerves". On the other hand, different responses to stress often accompany heavy drinking, as seen in alcohol use disorder. We are continuing to investigate whether stress causes excessive drinking, or vice versa.'

Developing Future Therapeutic Interventions

Dr Hwa's research highlights the links between stress, coping mechanisms and excessive alcohol consumption. Her work has suggested that responses to stress both precede heavy alcohol drinking as well as become changed as a consequence of it. Using preclinical models, this research has identified several targets for therapeutic interventions that could help reduce alcohol consumption as well as enhancing the stress coping mechanisms in people with alcohol use disorders.

Meet the researcher

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In 2015, Dr Lara Hwa received her PhD in Experimental Psychology from Tufts University in the USA. Following this, she completed her postdoctoral fellowship at the Bowles Center for Alcohol Studies at the University of North Carolina School of Medicine. In January 2021, Dr Hwa moved to Baylor University's Department of Psychology and Neuroscience where she was appointed as an Assistant Professor. Dr Hwa's research focuses on the cells and circuits underlying how stress interacts with long-term alcohol drinking, aiming to answer fundamental questions in behavioural neuroscience. In addition to her multiple research accolades, Dr Hwa has also been formally recognised for her outstanding mentorship of young researchers.

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FURTHER READING

L Hwa, A Chu, S Levinson, et al., Persistent escalation of alcohol drinking in C57BL/6J mice with intermittent access to 20% ethanol, Alcoholism: Clinical and Experimental Research, 2011, 35(11), 1938–47.

L Hwa, A Shimamoto, K Norman, et al., Dissociation of mu opioid receptor and CRF-R1 antagonist effects on escalated ethanol consumption and mPFC serotonin in C57BL/6J mice, Addiction Biology, 2016, 21(1), 111–124.

L Hwa, E Holly, J DeBold, K Miczek, Social stress-escalated intermittent alcohol drinking: modulation by CRF-R1 in the ventral tegmental area and accumbal dopamine in mice, Psychopharmacology, 2016, 233(4), 681–690.

L Hwa, S Neira, M Flanigan, et al., Alcohol drinking alters stress response to predator odor via BNST extended amygdala kappa opioid receptor signaling in male mice, eLife, 2020, 9, e59709.