CAPSTONE

Review of Drug Addiction and the Role of Perineuronal Nets

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Introduction

Drug addiction is a disease that is long-lasting and affects not only the physical but mental and psychiatric states of users, families, and communities.[1] Drug addiction is characterized by misuse and dependence of both illicit and prescription drugs, including but not limited to opioids, heroin, controlled prescription drugs, methamphetamines, and cocaine.[2] Since 2011, drug poisoning deaths have been the leading cause of injury-related death in the U.S.[2] In the U.S. alone, there are close to 192 deaths from drug overdose daily.[2] While treatments are available, most programs have a high rate of relapse, making it crucial to find better methods of reducing drug-seeking behaviors.[1]

Many studies on drug addiction focus on the reward circuitry within the brain. This circuitry relates drug-associated cues with the memories of previous drug use.[3,4,5] Because of this association, being in a similar environment as previous drug use will increase drug craving, therefore increasing the probability of continual drug use and relapse.[3,4,5] Because of the direct link between drug memories and addiction, many researchers focus on ways to block or reduce the strength of these memories. Recently, drug researchers have been shifting focus to a structure in the extracellular matrix (ECM), known as perineuronal nets (PNNs). PNNs are a net-like structure composed of proteoglycans that surround fast-spiking GABAergic interneurons throughout the brain.[3,6] These structures were discovered in 1898 by Camillo Golgi but were not intensely researched until about 80 years after.[7] More recently, it was found that PNNs were involved in learning, memory, and drug addiction.[3] Specifically, the stability of PNNs relates to the synaptic plasticity of the surrounding neurons and therefore to the stability of memories, especially drug memories.[6] In this review, I explore the role that PNNs play in drug addiction and relapse and its potential to better drug addiction treatment.

Pnns and their relation to learning and memories

The reward circuitry within the brain is highly studied for its role in addiction. This circuitry and its relation to memories can be simply explained by the original studies done by Ivan Pavlov on dogs.[5] This study involved pairing a bell ring with feeding times. After multiple pairings, the dogs associated the bell with food and began salivating more even if they were not given food immediately after the ring.[5] This same concept goes for other memories as well. The reward circuitry partially controls emotional responses and links them with memories.[8] Due to this association, the brain will recall emotions from previous memories when in the presence of similar stimuli.[9,10] PNNs are highly involved with the formation and maintenance of these memories. A recent study focused on the role of PNNs within the sensory cortex on fear learning and found that PNNs were necessary for the proper formation of fear memories.[11] Reduction of the intensity of PNNs also led to mice more easily forgetting fear memories.[3]

PNNs are regulated by changes in calcium conductance, potassium levels, and AMPA/NMDA receptor activity.[12] The structural integrity of PNNs is directly related to neuronal plasticity within that area of the brain or spinal cord.[3,4,12] While these structures are developing, plasticity of the surrounding neurons is high, allowing for formation and updating of memories.[3,11,12]

Drug-related memories and PNNs

PNNs have an important role in not only fear memories, but drug-related memories as well. Many studies use a cue-pairing and/or self-administration methods in animal models of drug addiction.[5] The cue-pairing method is much like the Pavlovian studies in which an environmental cue is associated with the emotions of a previous memory (in this case the euphoric feeling of the drug). Self-administration is a method in which animals press a lever at a random or fixed number of times to receive a drug reward. Previous studies have shown that knocking out (reducing intensity of) PNNs reduces drug-seeking behaviors in both cue-pairing and self-administration methods.[6,10,12] In the lateral hypothalamus, an important structure in the limbic system, the degradation of PNNs leads to decreased cue-induced reinstatement of cocaine-seeking behaviors.[10] To destroy these nets and increase neuronal plasticity, Chondroitinase-ABC (Ch-ABC) is commonly used. Ch-ABC is an enzyme that cleaves chondroitin sulfate glycosaminoglycan chains, a main structural component of PNNs.[13]

Even without the use of external enzymes, such as Ch-ABC, PNNs change with continual drug exposure. One study found that the intensity of PNNs decreased 2 hours after 1 day of cocaine exposure but increased after 5 days of exposure.[6] This likely reflects the changing of the memories after the first day of exposure and the increased integrity of memories after 5 days of exposure. During nicotine self-administration, PNN intensity in the ventral tegmental area (VTA) and orbitofrontal cortex (OFC) was decreased from 45 minutes to 72 hours after the last exposure, indicating a change in GABAergic interneurons in this area.[4] Prescribed drugs, such as monoamine reuptake inhibitors used for depressive symptoms, were shown to increase PNN-degrading matrix metalloproteinases (MMPs) and lead to a reduction in the integrity of PNNs, indicating that PNNs play a role in drug efficacy.[14]

Pnn-associated proteins and how they affect drug memories

The main proteins involved in the structure of PNNs are hyaluronic acid and chondroitin sulfate proteoglycans, including aggrecan and brevican.[12] PNNs are also co-localized with GABAergic Parvalbumin-positive (PV+) interneurons; around 60-80% of PV cells are surrounded by PNNs.[12] Some of the trends of PNNs are also applicable to its affiliated proteins. A decrease in PNN intensity is normally followed by a decrease in PV expression within cells.[10,12] In aggrecan knockout mice, cells were able to express PV but were unable to form PNNs.[3] Brevican levels were decreased in the mouse hippocampus after environmental enrichment and in brain tissue from patients with epilepsy, indicating that brevican has an influence on the activity of inhibitory neurons.[3] Aggrecan and brevican gene expression increased four hours after drug-conditioning along with intensity and number of PNNs.[3] These data indicate that multiple components of PNNs also play a similar role in regulating drug memories and could be targeted in manipulation studies.

Future directions/conclusion

Together, PNNs are a promising structure to explore when aiming to improve drug addiction treatments and reducing relapse rates. Research has shown a strong relationship between PNN intensity and drug-related memories. With either cocaine or nicotine addiction, the increase in memory strength was followed by an increase in PNN intensity. Knocking out PNNs using Ch-ABC led to a decrease in drug-seeking behavior in rodents. PNN-associated proteins, including brevican, aggrecan, and PV, also play a role in the integrity and intensity of PNNs and therefore affect the formation and updating of memories. Research has shown that multiple components of PNNs can alter memories, making PNNs and PNN-associated proteins promising targets in

possible drug therapy. Studies have shown that trends of PNNs, including increasing/decreasing intensity of PNNs, are followed by PNN-associated proteins (e.g. decrease in PNNs results in a decrease in PV expression). Future studies should focus on targeting and manipulating the expression of these proteins to determine their effect on drug-seeking behavior. Recent studies have also determined the effect of other cellular processes, such as oxidative stress, on the intensity of PNNs, but have failed to fully study how this process affects behavior as well. Due to the relationship between PNNs and drug efficacy, future studies should test the effects of combining prescription drugs, such as antidepressants, with a PNN-altering enzyme to determine if the efficacy changes.

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