

Restoration of Neuroprotection of Glial Cells in Opioid Addiction: Case Report

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Abstract

Opioid addiction is a global public health crisis that resulted from well-intentioned efforts by physicians to improve pain control in the 1990s. The lack of knowledge about the addictive tendencies of opioids have led to what is now known as the opioid epidemic that is causing a significant economic and social burden worldwide. Research has primarily focused on the behavioral components of addiction but has recently turned to examining the role of neurons and glial cells in regulating addiction. Glial cells have been shown to alter opioid pharmacodynamics through a proinflammatory response, ultimately leading to excitotoxicity, disruption of neural homeostasis, and hypersensitivity to pain. It is hypothesized that restoring the neuroprotective capacity of glial cells through targeted therapies will prevent further degeneration of neurons during chronic opioid abuse [1]. Nanoparticle delivery systems are a valuable tool in the fight against addiction due to their ability to carry a variety of payloads, penetrate biological membranes, and release the payload in a controlled manner. This perspective provides insight into the cellular mechanisms of addiction, adjusting our focus to highlight the role of glial cells in regulating opioid efficacy and the impact of addiction. Additionally, we discuss different pathways by which nanotherapeutics can be optimized to target and increase the neuroprotection of glial cells to reduce the burden caused by Opioid toxicity in people with chronic opioid dependence.

Keywords: Nanomedicine; Opioid crisis; Excitotoxicity; Toll-like receptor; Hyperalgesia; Glial cells

Introduction

Surrounded by stories of mystery and divine magic, opium has been used as an elixir for a variety of ailments, dating back to the beginning of human civilization. Extracted from the *Papaver somniferum* plant, what was once a pain treatment has now led to a global opioid crisis, affecting 35 million people worldwide and killing nearly 841,000 Americans over the past two decades. These addictive properties of opioids are due in part to the binding of opioids to mu(μ)-opioid receptors that exert their effects primarily on pain perception and the reward circuit structure of the central nervous system (CNS). Although opioids provide pain relief and euphoria, their side effects cannot be ignored. In addition to the physiological side effects of opioid abuse such as constipation, nausea, vomiting, respiratory depression, sedation, kidney damage, liver damage, and hormonal imbalance, addiction to opioids also causes unintended consequences. These include increased rates of transmission of hepatitis C virus and HIV among people who inject drugs, increased rates of crime and imprisonment among drug users, and neonatal abstinence syndrome (NAS) in infants.

Despite millennia of opioid use and decades of intensive research, the role of glial cells in facilitating addiction has only recently begun to be considered. They were previously thought to make up a significant portion of brain cells, but more recent studies demonstrate that the glia-to-neuron ratio may be closer to 1:1. Glial cells have long been underestimated in their ability to influence CNS cell signaling and their influence on the efficacy of xenobiotics. The focus here is on microglia and astrocytes, which protect and strengthen the central nervous system. Microglia are the resident immune cells of the nervous system, responsible for seeking out threats and generating specialized immune responses. Astrocytes play an important role in maintaining CNS homeostasis by supporting neurons and the structural integrity of the blood-brain barrier (BBB) [2-5]. Exogenous opioids alter the homeostatic environment of the central nervous system by inducing immune signaling events that limit the analgesic properties of opioids. Immunological phenomena such as the release of inflammatory

cytokines and chemokines through activation of Toll-like receptor 4 (TLR4) and mitogen-activated protein kinase (MAPK) are implicated in opioid tolerance, known as opioid-induced hyperalgesia (OIH). Astrocytes, exposed to prolonged stress from continuous opioid consumption, lose the ability to adequately remove excess glutamate from synapses. When combined with gamma-aminobutyric acid (GABA) inhibition, the imbalance leads to excitotoxicity and, in prolonged cases, neuronal degeneration. Such events increase pain sensitivity and reduce the neuroprotective capacity of glial cells, leaving the central nervous system vulnerable to acute extracellular changes with the potential to alter physiological and behavioral components in individuals with opioid use disorder. Opioids have also been shown to increase the BBB activity of P-glycoprotein, a protein that increases the flux of xenobiotics across the BBB, adding another layer of complexity to finding appropriate treatments for chronic opioid use.

Behavioral and cellular mechanisms of addiction

Drugs of abuse such as opioids have the unique ability to disguise themselves as prized targets of the brain, allowing the urge to become addictive. Changes caused by addiction, a medical condition characterized by compulsive drug use, manifest primarily through alterations in reward mechanisms that can persist for years even after cessation of narcotic use. Opioids are commonly used for pain control; however, they can also stimulate pleasure in the absence of pain.

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Opioids can bind to one of three types of inhibitory G protein-coupled receptors located primarily in the central nervous system, although they are also found in peripheral neurons and the gastrointestinal tract. The three types of receptors include mu, delta, and kappa, but the main receptor of concern when it comes to drug addiction is the mu receptor. Exogenous opioids bind to mu receptors, disinhibiting dopamine neurons through inhibition of GABAergic neurons. This event then triggers the release of dopamine (DA) from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), two key components of the reward pathway, to produce feelings of pleasure.

Microglia and their role in the CNS

While decades of research have focused on the effects of opioids on neurons, glial cells may also play an important role in regulating addiction. Microglia, comprising approximately 15% of CNS cells, are specialized phagocytic cells of the CNS. They function as investigators of the CNS and are responsible for searching for threats such as bacteria, parasites, toxins, and xenobiotics and generating specialized immune responses. Microglia are equipped with an arsenal of specialized responses such as phagocytosis, degradation through lysosomes, and release of cytokines to attract other immune cells or induce apoptosis if necessary. Although they were once thought to operate on a reactionary basis, becoming active only during invasion, studies have shown that microglia actively extend their processes to networks of microglia and neurons around to ensure homeostasis. Effects of opioids on astrocytes

Often characterized as star-shaped cells of the CNS, astrocytes perform a multitude of functions such as maintaining water and homeostasis, protecting against internal stress responses, mitochondrial biogenesis, tissue repair and synaptic modulation. Astrocytes, like microglia, also play an important immunological role in the central nervous system [6]. When activated, astrocytes release chemokines and cytokines that alter the extracellular environment in the central nervous system to induce a series of changes in neurons and surrounding cells.

Opioids cause stimulant toxicity and neurodegeneration in the central nervous system

Astrocytes are the main regulatory agents of the central nervous system, forming up to 30,000 connections with neighboring cells. Glutamate, the most common excitatory neurotransmitter, is involved in opioid pharmacodynamics and is regulated by astrocytes. Under normal circumstances, residual extracellular glutamate is actively transported out of the synapse by astrocytes. Using two transporters EAAT1 and EAAT2, astrocytes absorb excess glutamate to optimize nerve function [7,8]. Under the influence of opioids, the function and

expression of glutamate transporters are altered, leading to acute and chronic homeostasis disorders.

Conclusion

Opioid addiction is a complex, multifaceted disease rooted in genetic, behavioral, biological, and social factors. Opioids still have the best pain relief; However, the serious consequences of prolonged opioid use cannot be ignored. As researchers work to synthesize non-addictive pain relievers, solutions are needed to minimize the effects of chronic opioid use and opioid dependence. It is in this context that nanomedicine can succeed by providing targeted drug delivery, prolonging drug half-life and reducing toxicity. Through the activation of microglia and astrocytes, opioids paradoxically induce greater pain sensation in the individual. In summary, initiation of immune cascades leads to neurodegeneration, increased BBB permeability, and disruption of neural homeostasis. Such effects work to neutralize opioid effects, increase tolerance, and promote dependence. Much work remains to be done to alleviate pain in individuals and develop treatments that reduce the risk of addiction, but in the meantime, the versatile properties of the nanoplatform, with its ability to cross the BBB and accumulates in glial cells, which may serve as a therapeutic approach to alleviate neurodegeneration in patients with opioid abuse.

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