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GLIAL CELLS RESPONSES: IN OPIOID WITHDRAWAL SYNDROME

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ABSTRACT: Drug addiction represents one of the major medical, social, and economic burdens of human behavior. Opioids are powerful relievers; use of opioids for the treatment of pain has been associated with the potential disadvantages including development of tolerance, dependence. There are seven stages involved in opioid addiction. Identification of glial-mediated mechanism inducing opioid side effects includes cytokine receptor, κ-opioid receptor, NMDA receptor and toll like receptor (TLR). Glial activation through TLR leading to the release of proinflammatory cytokines acting on neurons which is important in the complex syndrome of opioid dependence and withdrawal. Moreover, newer agents targeting these glial cell activation such as AV411, AV33, SLC022 and older agents for other diseases conditions such as minocyclline, pentoxifylline, all show varied but promising profiles for providing significant relief from opioid side effects.

INTRODUCTION: Opioids are standard drugs used to manage severe pain and are the most commonly used psychoactive substances across the world [1, 2, 3]. It is kind of chronic relapsing brain diseases characterized by the loss of control over intake [4, 5, 6]. Acute morphine along with other opioid withdrawal proceeds through a number of stages. There are seven stages which are involved in withdrawal syndrome.

Various receptors are involved in opioid withdrawal like mu, kappa, delta, glutamate and toll like receptors (TLR). There are various types of TLR in which some are play important role in opioid withdrawal.

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Recent studies reveal that TLRs, including TLR2 AND TLR4, a key link between the innate immune system and CNS [7, 8].

Glial cells are important for structural and metabolic maintenance of the nervous system, there are numerous reports demonstrating the ability of glial to respond to and send signals to neurons and synapses in the central and peripheral nervous system (CNS and PNS) [9].

Opioid induced proinflammatory glial activation has been inferred from:

a) Morphine induced upregulation of mircoglial [10, 11] and astrocytes [11, 12].

b) Morphine induced upregulation and/ or released proinflammatory cytokines [11, 13, 14, 15, 16, 17, 18].

c) Enhanced morphine analgesia by co-administering the microglial attenuators

minocycline [10, 13, 14, 15] or AV411 [11] and the astrocytes inhibitor fluorocitrate [12].

d) Enhanced morphine analgesia by blocking proinflammatory cytokine action [13, 14, 19].

e) Opioid induced selective activation of microglial p38 MAPK and associated enhanced morphine analgesia [10].

As such, opioid induced proinlammatory glial activation through TLR is characterized by a cellular phenotype of enhanced reactivity and propensity to proinflammation in response to exposure of glial to opioids [13, 14, 15].

The research on glial cells, glial cells supply nerve fibres with energy rich metabolic products and glial cells assist in the repair of injured nerves.

Stages involved in Opioid withdrawal:

- Stage I: Six to fourteen hours after last dose: Drug craving, anxiety, irritability, perspiration, and mild to moderate dysphoria.
- Stage II: Fourteen to eighteen hours after last dose: Yawning, heavy perspiration, mild depression lacrimation, crying, running nose, dysphoria, also intensification of the above symptoms. "yen sleep" (a waking trance-like state)
- Stage III: Sixteen to twenty-four hours after last dose: Rhinorrhea (runny nose) and increase in other of the above dilated pupils, piloerection (gooseflesh), muscle twitches, hot flashes, cold flashes, aching bones and muscles, loss of appetite and the beginning of intestinal cramping.
- Stage IV: Twenty-four to thirty-six hours after last dose: Increase in all of the above including severe cramping and involuntary leg movements ("kicking the habit"), loose stool, insomnia, elevation of blood pressure, moderate elevation in body temperature, increase in frequency of breathing and tidal volume, tachycardia (elevated pulse), restlessness, nausea.
- Stage V: Thirty-six to seventy-two hours after last dose: Increase in the above, fetal position, vomiting, free and frequent liquid diarrhea, which sometimes can accelerate the time of passage of food from mouth to out of system to an hour or less, involuntary ejaculation, which is often painful, saturation of bedding materials with bodily fluids, weight loss of two to five kilos per 24 hours, increased white cell count and other blood changes.
- Stage VI: After completion of above: Recovery of appetite ("the chucks"), and normal bowel function, beginning of transition to post-acute and chronic symptoms that are mainly psychological but that may also include increased sensitivity to pain, hypertension, colitis or other gastrointestinal afflictions related to motility, and problems with weight control in either direction (Chan *et al*., 1999) [20].

Receptors involved in Opioid withdrawal syndrome: Opioid receptors are a group of G proteins coupled receptors with opioids as ligands. Opiate receptors are distributed widely in the brain and are found in spinal cord and digestive tract [21, 22, 23].

The four major subgroups of opiate receptors are delta (δ), kappa (κ), mu (μ) and nociception and each is involved in controlling different function in the brain[24]. For example: opiates and endorphins block pain signal by binding to the μ receptor site. The δ receptor in the brain is involved in pain relief, antidepressant effects and physical dependence.

The κ receptor in the brain and spinal cord are linked with sedation, spinal analgesia and pupil constriction. The function of the μ receptor in the brain and spinal cord are physical dependence, respiratory depression, euphoria, pupil constriction and supraspinal analgesia.

Nociception receptors in the brain and spinal cord are involved with appetite, depression, anxiety and the development of tolerance to μ agonists (**Table 1).**

TABLE 1: **RECEPTORS INVOLVED IN OPIOID WITHDRAWAL SYNDROME**

Receptors	Subtypes	Location[25,26]	Function [25, 26]
Delta (δ) DOP OP1	Δ1 δ_2	Brain Pontine nuclei Amygdale Olfactory bulbs Deep cortex Peripheral sensory neurons	Analgesia Antidepressant effects Physical dependence
Kappa (κ) KOP OP2	κ1 κ2 κ3	Brain Hypothalamus Periqueductal gray Claustrum Substantia gelatinosa Peripheral sensory neurons	Analgesia Sedation Miosis Inhibition of ADH release Dysphoria
Mu (μ) MOP OP3	μ1 μ2 μ3	brain cortex thalamus striosomes periqueductal gray intestinal tract	μ1:- analgesia physical dependence μ2:- respiratory depression miosis euphoria reduced GI motility physical dependence μ3:- possible vasodilation

Involvement of Glutamate receptors in Opioid withdrawal Syndrome:

- Types of glutamate receptors: Glutamate is one of the most abundant excitatory neurotransmitters in the central nervous system. Once released into the synaptic cleft, glutamate can bind to its receptors and exert its effect. According to pharmacological and molecular biological classification, glutamate receptors can be divided into two categories, ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs).

- The role of glutamate and its receptor in opioid addiction: It is known that certain glutamatergic projection could be impacted by addictive drugs. Data indicate that the activation of glutamatergic efferent fibers from the amygdala and prefrontal cortex is critical in the expression of addictive behaviors [27, 28, 29, 30, 31, 32]. The alteration of glutamate-mediated transmission, especially the increase of glutamatergic transmission in the NAc may promote the seeking and relapse from abused drugs [33, 34, 35, 36]. Microinjection of glutamate into the VTA can increase exploratory motor behaviors and the release of DA in NAc and mPFC. These results suggest that glutamate plays an important role in opioids dependence.

- The role of iGluRs in opioid addiction [37]. NMDA receptors in rat brain following long-term treatment with morphine. Then it was shown that the expression of NMDA receptors was upregulated in morphine-dependent rat brains [38]. Recently, more studies showed that glutamatergic signal transduction can regulate drug effects, resulting in drug tolerance and dependence, including the tolerance and dependence of opioids. Glutamatergic afferents play a key role in regulating the firing of the VTA neurons. Activation of glutamatergic afferents and the VTA infusion of glutamate receptor agonists increase the firing rates of dopaminergic neurons and induce burst firing *in vivo* [39, 40, 41].

  It was also demonstrated that MK801, an NMDA receptor antagonist, completely blocked the withdrawal symptoms induced by glutamate and naloxone [42, 43]. MK-801 can also decrease morphine dependence, which may be related to the downregulation of NMDA receptors [37, 38]. Western blot and microdialysis results showed that chronic intermittent use of morphine, cocaine and other addictive drugs can increase the level of glutamate in the VTA, upregulating the expression of AMPA receptor subtypes GluR1 and NMDAR1 in the VTA [44, 45].

Co-application of opioids and NMDA receptor competitive or non-competitive antagonists can block the pain tolerance and physical dependence of opioid and the drug-seeking behaviors [46].

Glutamatergic signal transduction mediated by NMDA receptors was involved in the formation and maintenance of morphine dependence in human [47]. So that glutamate released in the central nervous system plays an important role in opioid withdrawal behaviors and that the iGluRs are involved in the process.

- **The role of mGluRs in opioid addiction**: Metabotropic glutamate receptors, which mediate slow glutamate neurotransmission, are located throughout the limbic and cortical brain regions implicated in drug addiction. There is significant pharmacological and behavioral evidence that group I mGluRs are widely distributed in the projection neurons and intermediate neurons in the shell and core of NAc, providing the morphological evidence for their regulation and therapic effects in reward-related behaviors and drug addiction [48, 49].

3-[(2- methyl-1, 3-thiazol-4-yl)ethynyl] pyridine (MTEP), an mGluR5 antagonist, dose-dependently inhibited morphine withdrawal symptoms induced by naloxone [50]. DA and glutamate play critical roles in the induction of LTP in the NAc through the activation of D1 dopamine receptors and group I mGluRs [51]. It was reported that the number and function of group II mGluRs upregulated the formation of opioids withdrawal.

Group II mGluRs (mGluR2 and mGluR3) were involved in the negative regulation in the brain reward circuit and the formation of conditional offensive responses in drug dependence and withdrawal. However, the role of group III mGluRs in drug dependence is still not well investigated. Further investigation is required to fully understand the role of mGluRs in the pathological process of drug addiction.

Toll like Receptors: TLRs, a family of evolutionarily conserved pathogen recognition receptors, play a pivotal role in innate immunity. TLR family consists of 13 mammalian members. The cytoplasmic portions of TLRs show high similarity to that of the interleukin-1 receptor (IL-1R) family and are now called the Toll/IL-1 receptor (TIR) domain. A TIR domain is required to initiate intracellular signaling. The extracellular regions of TLRs and IL-1R are markedly different. Whereas IL-1R possesses an Ig-like domain, TLRs contain leucine-rich repeats in their extracellular domains.

TLRs are pattern recognition receptors that sense a wide range of microorganisms, such as bacteria, fungi, protozoa, and viruses. Each TLR has its own intrinsic signaling pathway and induces specific biological responses against microorganisms such as dendritic cell maturation, cytokine production, and the development of adaptive immunity [52].

Glial Cells: Glial cells, also called neuroglia or simply glia are non-neuronal cells that maintain homeostasis, form myelin and provide support and protection for neurons in the brain. Glial cells comprise 90% of the human brain [53].

Types of Glial Cells: Glia are divided into two subtypes, the microglia which function largely as scavengers to engulf apoptotic cell debris and the macroglia comprised of oligodendrocytes that myelinate axons, and astrocytes [54].

- **Microglia**: Microglia's are specialized macrophages capable of phagocytosis that protect neurons of the central nervous system [55]. They are derived from hematopoietic precursors rather than ectodermal tissue; they are commonly categorized as such because of their supportive role to neurons. These cells comprise approximately 15% of the total cells of the central nervous system. They are found in all regions of the brain and spinal cord. Microglial cells are small relative to macroglial cells, with changing shapes and oblong nuclei. They are mobile within the brain and multiply when the brain is damaged. In the healthy central nervous system, microglia processes constantly sample all aspects of their environment (neurons, macroglia and blood vessels) (**Table 2**).

TABLE 2: MACROGLIA

Location	Name	Description
CNS	Astrocytes	The most abundant type of macroglial cell, astrocytes (also called astroglia) has numerous projections that anchor neurons to their blood supply. They regulate external chemical environment of neurons by removing excess ions, notably potassium, and recycling neurotransmitters released during synaptic transmission. The current theory suggests that astrocytes may be the predominant "building blocks" of the blood–brain barrier. Astrocytes may regulate vasoconstriction and vasodilation by producing substances such as arachidonic acid, whose metabolites are vasoactive. Astrocytes signal each other using calcium. The gap junctions (also known as electrical synapses) between astrocytes allow the messenger moleculeIP3 to diffuse from one astrocyte to another. IP3 activates calcium channels on cellular organelles, releasing calcium into the cytoplasm. This calcium may stimulate the production of more IP3. The net effect is a calcium wave that propagates from cell to cell. Extracellular release of ATP, and consequent activation of purinergic receptors on other astrocytes, may also mediate calcium waves in some cases. In general, there are two types of astrocytes, protoplasmic and fibrous, similar in function but distinct in morphology and distribution. Protoplasmic astrocytes have short, thick, highly branched processes and are typically found in gray matter. Fibrous astrocytes have long, thin, less branched processes and are more commonly found in white matter. It has recently been shown that astrocyte activity is linked to blood flow in the brain, and that this is what is actually being measured in fMRI [56]. They also have been involved in neuronal circuits playing an inhibitory role after sensing changes in extracellular calcium [57].
CNS	Oligodendrocytes	Oligodendrocytes are cells that coat axons in the central nervous system (CNS) with their cell membrane forming a specialized membrane differentiation called myelin, producing the so-called myelin sheath. The myelin sheath provides insulation to the axon that allows electrical signals to propagate more efficiently [58].
CNS	Ependymal cells	Ependymal cells, also named ependymocytes, line the cavities of the CNS and make up the walls of the ventricles. These cells create and secrete cerebrospinal fluid (CSF) and beat their cilia to help circulate the CSF and make up the Blood-CSF barrier. They are also thought to act as neural stem cells [59].
CNS	Radial glia	Radial glia cells arise from neuroepithelial cells after the onset of neurogenesis. Their differentiation abilities are more restricted than those of neuroepithelial cells. In the developing nervous system, radial glia functions both as neuronal progenitors and as a scaffold upon which newborn neurons migrate. In the mature brain, the cerebellum and retina retain characteristic radial glial cells. In the cerebellum, these are Bergmann glia, which regulate synaptic plasticity. In the retina, the radial Müller cell is the principal glial cell, and participates in a bidirectional communication with neurons [60].
PNS	Schwann cells	Similar in function to oligodendrocytes, Schwann cells provide myelination to axons in the peripheral nervous system (PNS). They also havephagocytotic activity and clear cellular debris that allows for regrowth of PNS neurons [61].
PNS	Satellite cells	Satellite glial cells are small cells that surround neurons in sensory, sympathetic and parasympathetic ganglia [62]. These cells help regulate the external chemical environment. Like astrocytes, they are interconnected by gap junctions and respond to ATP by elevating intracellular concentration of calcium ions. They are highly sensitive to injury and inflammation, and appear to contribute to pathological states, such as chronic pain [63].
PNS	Enteric glial cells	Are found in the intrinsic ganglia of the digestive system. They are thought to have many roles in the enteric system, some related to homeostasis and muscular digestive processes [64].

Glial in the Central Nervous System: In the central nervous system (CNS), consisting of the brain and spinal cord, the major glial types are astrocytes and oligodendrocytes. The astrocytes, which are more numerous, have many radiating processes that interweave in complex and intimate ways between neuronal cell bodies and fibres.

Some astrocyte processes contact blood vessels and may control the blood-brain barrier which protects the CNS from unwanted substances in the general circulation. Others form cuffs or veils around individual synapses, and synaptic transmission can be modified by signals between nerve terminals and these glial elements.

They also have high affinity uptake sites for major brain neurotransmitters that help to remove excess transmitter following release from nerve terminals. Together this provides compelling evidence that gial cells are directly involved in information processing in the brain. Astrocytes also help to control the levels of potassium in the extracellular space and have major roles in CNS development.

Oligodendrocytes form one of the most highly specialized cellular structures in the body, the myelin sheath, which forms electrical insulation around nerve fibres thereby making rapid transmission of electrical signals in the brain possible. The CNS also contains microglia, resident, macrophage-like cells that originate from blood monocytes rather than the neurectoderm.

Glial in the Peripheral Nervous System: In the peripheral nervous system (PNS), the major glial cells are Schwann cells. They ensheath all axons in peripheral nerves and are found in two types, myelinating and non-myelinating. The myelinating Schwann cells form insulating sheaths around axons that are comparable in structure and function to those made by oligodendrocytes in the CNS. The non-myelinating cells show similarities with astrocytes and are likely to have metabolic and mechanical support functions. There is evidence that Schwann cells are indispensable for neuronal survival during development, and in damaged nerves Schwann cells control successful regeneration and restoration of function.

Olfactory ensheathing cells represent a special category of glia that resembles non-myelinating Schwann cells and associate with both the CNS and PNS part of the primary olfactory axons. Another important category of PNS glia is the enteric glia. They are found in the autonomic ganglia of the gut (the enteric nervous system). Unlike other parts of the PNS, the enteric system has complex synaptic interactions and high integrative capacity, and the enteric glia is remarkably like astrocytes in structure and biochemistry. The cell bodies of other autonomic ganglia and sensory ganglia are enveloped by simpler satellite glial cells, while the synapses between nerve terminals and skeletal muscle are covered by terminal glia, also called teloglia or perisynaptic glia. They help to maintain a stability of the neuromuscular junction and regulate synaptic transmission [65].

Role of Microglia in Opioid Withdrawal: Microglial cells like other cells of immune system lineage display functional opioid receptors [66, 67]. Overstimulation of these receptors can lead to apoptosis of microglial cells [68]. Methamphetamine administration to rats at doses that induce dependence causes activation of microglial cells in the striatum. Since the activation of microglia follows a course similar to the neurotoxicity caused by METH, it has been suggested that METH neurotoxicity might be at least in part mediated by the METH-activated microglia [69, 70]. Also attenuation of microglial activation mediates tolerance to the neurotoxicity of METH in the striatum[71]. Microglia activity might also be involved in the mediation of the behavioral effects of METH because, in rats, minocycline (an anti-inflammatory known to affect microglia) treatment not only reduced damage to dopaminergic terminals but also significantly attenuated behavioral sensitization caused by repeated administration of METH [72].

Role of Astrocytes in Opioid Withdrawal: Astrocytes are the most abundant glial cell type in the central nervous system[73]. Like other glial cell types, astrocytes were once thought to play only a secondary, non-regulatory and permissive role in nervous function. The cell membranes of astrocytes bear receptors for most neurotransmitters and peptides: glutamate, dopamine, norepinephrine, serotonin, gammaaminobutyric acid, acetylcholine and opioid peptides [74]. They also bear in their plasma membranes neurotransmitter [75, 76, 77] and glucose [78] transporters, and aquaporin-4 channels for water transport [79, 80].

Administration of cocaine, amphetamines and most psychostimulants induces activation of astrocytes[81, 82, 83]. This activation is defined by an increase in the expression of glial fibrillary acidic protein (GFAP), a main component of the cytoskeleton of astrocytes. GFAP is known to be upregulated in response to brain injury and neurotoxicity [84, 85], although changes in GFAP expression are not limited to overt brain injury and many other plastic changes in the neuropil also result in increased GFAP expression [86, 87, 88]. For instance, treatment with ethamphetamine (METH, “speed”) results in loss of dopaminergic terminals without detectable loss of neurons [89], but induces astrogliosis with increased GFAP in the striatum, hippocampus and frontal cortex [90].

Chronic treatment with morphine also results in increased GFAP expression or enlarged astrocytes in VTA, NAcc, frontal cortex, locus coeruleus and nucleus of the solitary tract of the rat [91, 92, 93, 94, 95]. The morphine-induced increases in GFAP expression and the astroglial activation are probably mediated by a2-adrenoceptors since the antagonist yohimbine inhibits upregulation of a2-adrenoceptors and prevents the increase in GFAP expression caused by chronic morphine treatment [94, 95]. The responsiveness of astrocytes of morphine administration [96, 97] that astrocytes might contribute to morphine tolerance and more recent evidence supports that hypothesis [98].

For instance, inactivation of astrocytes by the gliotoxin fluorocitrate attenuates both tolerance to morphine analgesia and morphine-induced increase in GFAP immunostaining [93]. Tolerance to morphine has been also related to downregulation of glial glutamate transporters GLT-1 and GLAST in the spinal cord [99] suggesting a link between structural and functional features of astrocytes involved in tolerance to morphine.

The neurotrophic activity of astrocytes may also be relevant to the effects of cocaine in VTA. Glial-derived neurotrophic factor (GDNF) is present in neurons astrocytes and microglial cells, although it seems to be mainly produced by astrocytes [100, 101]. GDNF supports the survival and differentiation of dopaminergic cells and protects those cells against METH-induced neurotoxicity as shown in wild-type mice [102] and in heterozygous mice with a partial deletion of the GDNF gene [103]. Glial-derived neurotrophic factor, when infused into the VTA reduces the increase in the formation of key proteins induced by cocaine exposure [104]. Furthermore mice lacking expression of GDNF display increase behavioral sensitization to cocaine [105] and treatment of mice with the dipeptide Leu-Ileu an inducer of GDNF (and TNF-alpha, also produced by astrocytes) expression blocked the acquisition of METH-induced place preference and sensitization [106, 107].

Tumor necrosis factor alpha, produced by astrocytes and microglial cells, has been shown recently to prevent METH neurotoxicity and dependence in mice possibly through the enhancement of dopamine uptake in the striatum and the prevention of METH-induced increases in extracellular dopamine [108].

Expression of TLRS in CNS Glial cells: Microglia are CNS tissue resident macrophages and act as immune sentinels of the brain. In accordance with this view, primary microglia *in vitro* constitutively expresses a wide complement of TLRs (TLRs1-9) at varying levels [109, 110]. In comparison, primary astrocytes also express a wide variety of TLRs, but at lower levels. Murine astrocytes express TLRs1-9, with particularly high levels of TLR3 [111, 112], suggesting that astrocytes may be particularly important for anti-viral responses in the CNS. To date, human astrocytes have been reported to express TLRs1-5 and TLR9, also with particularly high expression of TLR3 [109, 113, 114].

The lack of TLR6-8 may be a difference between species or the result of varying isolation and culture conditions. There is also evidence that both oligodendrocytes and neurons can express TLRs, but their role in innate immune responses during CNS [109, 115, 116]. Under resting conditions in vivo. Constitutive expression of TLRs is primarily in microglia and largely restricted to the circumventricular organs (CVOs) and meninges, areas with direct access to the circulation, although they may be expressed at lower levels in other regions as well [117, 118, 119].

The levels of TLRs in the CNS can be upregulated by viral and bacterial infection, treatment with TLR stimuli, or CNS autoimmunity [109, 112, 119, 120], providing a mechanism for amplification of inflammatory responses to pathogens infecting the CNS. These stimuli upregulate multiple TLRs in a coordinated fashion, not only the TLR involved in recognition of a particular pathogen or class of pathogens. For example, treatment of astrocytes with the dsRNA synthetic mimic polyinosinic-polycytidylic acid (poly I: C), a viral stimulus, upregulates its own receptor TLR3, and also upregulates TLR2 and TLR4, which are normally used to recognize bacterial product [111].

Similarly, infection of mice with rabies broadly increases CNS expression of TLRs1-4 and 6–9[112].The pattern of TLR upregulation is not fixed and varies with the particular pathogen encountered, even with pathogens of a similar class. For example, in contrast to rabies virus, Semliki forest virus infection in the CNS fails to upregulate TLR4 and TLR6, but does increase expression of TLR13 [112].

The upregulation of TLRs in the CNS is likely in part due to the infiltration of TLR-expressing inflammatory cells, and in part due to the upregulation of receptor expression on astrocytes and microglia, which occurs in response to a variety of inflammatory stimuli [110, 111].

TLR Signalling mediators Glial cells activation in the CNS: Innate immunity in the cns depends primarily on the function of glial cells, especially in microglia which are important for the activation of adaptive system [121].

- **TLR in Microglia**: TLR mediated signalling promotes the production of a variety of inflammatory mediators [122, 123]. Exogenous and Endogenous TLR ligands activate microglial cells. TLR may mediate different pathway in microglial leading to either neuroprotective or neurotoxic phenotype1 [24]. However, activated microglia with TLR ligands also produce neurotoxic molecules such as nitric oxide (NO), reactive oxygen species (ROS), peroxynitriate, proinflammatory cytokines (TNF-α, IL-1β) which leads to withdrawal syndrome [125].

  TLR appear to activate very similar signaling pathways to IL-1 and some researchers now refer to this pathway as the TLR-IL signaling pathway[126]. That is, TLRs work through activation of an adaptor protein known as myeloid differentiation factor 88 (MyD88). This factor leads to activation of the IL-1 receptor-associated kinases (IRAKs) and TNF receptor – associated factor-6 (TRAF6), which finally culminates in activation of NF-Kb [127]. Other TLR- associated pathways include the JNK and interferon (IFN) pathways. Both TLR2 and TLR4 are important in recognizing endogenous pain-mediating signals. These studies have shown a highly interconnected web of pathway involving TLRs and other well–defined proinflammatory pathways which are associated with glial activation and opioid side effects [128, 129].

Relation between Glial cells and Proinflammatory cytokines: Glial cells of the CNS such as astrocytes, oligodendrocytes and microglia can respond to and also produce many of the proinflammatory cytokines initially attributed to lymphocytes and macrophages. These cytokines include IL-1, IL-2, IL-3, IL-4, IL-6, IL-8, IL-10, IFN-α, IFN-β, IFN-γ, TNF-α, TNF-β, TGF-β and colony sti ulating factor (CSFs) [130]. Opioid withdrawal induces glial activation and proinflammatory cytokines (TNF-α) expression in different sites of the brain.

Medications with potential for use as Opioid adjuncts:

- Ibudilast (AV411) is a blood-brain permeable, nonspecific phosphodiesterase inhibitor that acts centrally by attenuation of glial cell activation and reduction of proinflammatory activating factors, such as cytokines (TNF-α, IL-1β), nitric oxide, and chemokines such as monocyte schemo-attractant protein-1 and fractalkines; it increases production of anti-inflammatory IL-10[131,132]. It was initially used to treat bronchial asthma and poststroke dizziness, which has been attributed to its ability to reduce inflammation and cause vasodilatation [133].

  AV411 also reduces mechanical allodynia caused by neuropathic pain as well as noxious neuropathy induced by chemotherapeutic agents (paclitaxel and vincristine); it also reduces morphine tolerance. When administered systemically, AV411 was shown to be distributed to the spinal cord and to attenuate morphine induced glial cell activation in certain brain regions. AV411 has also been shown to inhibit peripheral inflammatory cells [134, 135], which have been suggested as a possible cause of reduced pain perception peripherally.

  AV411 also reduces spontaneous opioid withdrawal, protected naloxone-induced morphine withdrawal when given during the period of development of morphine dependence, and simultaneously enhanced analgesic effects [136]. These effects were seen with both morphine and oxycodone, with no changes in plasma morphine levels. Another study shows that AV411 decreases a morphine-induced increase of dopamine in the nucleus accumbens, a nucleus known to be associated with morphine-induced drug reward as well as withdrawal [137, 138].

- Dizocilpine (MK-801) is an NMDA-positive glutamate receptor noncompetitive antagonist that attenuates opioid tolerance and does not

influence the antinociceptive effects of morphine. When injected intrathecally, it decreases morphine tolerance at the spinal level[139]

- Propentofylline (SLC022) is an orally available, blood-brain permeable, methylxanthine derivative that acts as a glial inhibitor which attenuates neuropathic pain states as well as chemotherapy-induced painful neuropathy [140]. It decreases allodynia, possibly through altering γ-aminobutyric acid (GABA)ergic tone through modulation of glutamic acid decarboxylase in the spinal cord after injury, as well as reducing an injury-induced increased expression of GFAP [141]. Intraperitoneal injections of propentofylline attenuated condition-placed preference, a measure of drug reward in animals that were dependent on methamphetamine and morphine; this attenuation is thought to be caused by astrocytic activation [142]. Propentofylline also act as a neuroprotective agent in ischemia models [143].

- AV333 is a plasmid that has been shown to be a well-tolerated and effective antineuropathic agent when injected intrathecally. It functions as a glial cell inhibitor and promotes an increase in the amount of the anti-inflammatory cytokine IL-10 in the spinal cord

- Minocycline is a semisynthetic, second-generation broad spectrum, blood-brain barrier permeable tetracycline that has been historically used for its antimicrobial properties. However, it possess neuroprotective effects with reported benefits in experimental models of neurodegenerative disease, traumatic brain injury, and cerebral ischemia. Minocycline's protective role occurs by suppression of the mitochondrial permeability transition, inhibition of caspace-1 and -3 expressions and inhibition of microglial activation and proliferation [144] via antihyperalgesic and antiallodynic effects [145, 146].

  Minocycline inhibits the activation of microglial cells, which are thought to initiate neuropathic pain, thus preventing development of neuropathic pain in animal models. However, once these cells are activated, minocycline does not seem to be as effective in reducing pain states[146]. Although minocycline enhances the analgesic efficacy of opioids, it may also increase undesirable effects of opioids such as respiratory depression and drug dependence.

  Minocycline is a p-glycoprotein (p-gp) inhibitor, and inhibition of p-gp can cause altered pharmacokinetics of opioids, thus leading to increased bioavailability and ultimately an increase in adverse effects.

- Pentoxifylline is an inhibitor of glial activation, nonspecific cytokine synthesis, and phospho-diesterase (PDE) [147]. Pentoxifylline inhibit the production of mRNA and protein levels of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6, which were associated with reduced neuropathic pain [148] and inflammatory pain [149]. Along with reduction of these cytokines through inhibition of NK-κB, attenuation of pain symptoms has also been shown to be associated with elevated levels of the anti-inflammatory cytokine, IL-10, in the CNS [150].

Similar to AV411's inhibition of PDE, pentoxifylline reduces cyclic adenosine monophosphate (cAMP) levels, and this in turn results in decreased TNF-α and IL1-β production by microglia. These cytokines cause upregulation of nitric oxide synthase, which increases nitric oxide (NO) levels. NO is known to affect dopamine levels in the mesolimbic system, where increased dopamine levels are associated with opioid reward. Thus, these PDE inhibitors can potentially modulate drug reward and dependence [151].

Another suggested mechanism of attenuating morphine reward relates to a reduced production of adenosine by limited cAMP hydrolization. Adenosine causes inhibition of the inhibitory GABA pathways, which modulate pathways in the ventral tegmental area (VTA) of the mesolimbic system. The VTA contains cells that project to the nucleus accumbens and are a source of dopamine. Therefore, with reduced adenosine levels by PDE inhibitors, there may be attenuation of morphine reward through decreased dopamine in the nucleus accumbens and activation of cells in the VTA as well as glial cells[151]. In conclusion, pentoxifylline attenuates neuropathic pain states and may also contribute to reduction of morphine-induced tolerance and reward

Research on Glial Cells:

- **Glial cells supply nerve fibres with energy-rich metabolic products. Glial cells pass on metabolites to neurons**: Around 100 billion neurons in the human brain enable us to think, feel and act. They transmit electrical impulses to remote parts of the brain and body via long nerve fibres known as axons. This communication requires enormous amounts of energy, which the neurons are thought to generate from sugar. Axons are closely associated with glial cells which, on the one hand, surround them with an electrically insulating myelin sheath and, on the other hand support their long-term function. Klaus Armin and his research group from the Max Planck Institute of Experimental Medicine in Göttingen have now discovered a possible mechanism by which these glial cells in the brain can support their associated axons and keep them alive in the long term.

- **Glial cells assist in the repair of injured nerves**: When a nerve is damaged, glial cells produce the protein neuregulin1 and thereby promote the regeneration of nerve tissue. Unlike the brain and spinal cord, the peripheral nervous system has an astonishing capacity for regeneration following injury. Researchers discovered that, following nerve damage, peripheral glial cells produce the growth factor neuregulin1, which makes an important contribution to the regeneration of damaged nerves.

CONCLUSION: Opioid addiction, a significant and social problem is complicated by the phenomena of tolerance and dependence. There are various receptors which are involved in opioid withdrawal like glutamate receptors, κ-opioid, and toll like receptor (TLR). Glial activation via TLR increases the proinflammatory cytokines (TNF-α) causes the opioid withdrawal syndrome.

Hence, suppression of glial cells proinflammatory cytokines through TLR can significantly reduce opioid withdrawal syndrome. There are number of exciting directions for the use of glial-modifying agents as opioid adjuncts for the treatment of withdrawal syndrome. It appears that basic and clinical research involving both previously discovered agents such as Minocycline, pentoxifylline as well as newer agents such as AV411 and SLCO22.

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