Univerzita Karlova v Praze
Přírodovědecká fakulta

Studijní program: Biologie

Studijní obor: Molekulární biologie a biochemie organismů

Mária Stratilová

The role of neuroglia in the development of drug dependence

Úloha neuroglie v mechanismu vzniku drogové závislosti

Bakalářská práce

Vedoucí práce: doc. RNDr. Jiří Novotný, DSc.

Praha, 2014

Prohlášení:

Prohlašuji, že jsem závěrečnou práci zpracoval/a samostatně a že jsem uvedl/a všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

V Praze, 20.8.2014

……..

Mária Stratilová

Poďakovanie

Týmto by som chcela poďakovať môjmu školiteľovi doc. RNDr. Jiřímu Novotnému, DSc. za veľkú trpezlivosť, rady a pripomienky pri písaní tejto práce. Rovnako aj môjmu priateľovi Tomášovi Hundžovi a mojej rodine.

Content

1. Abstract

Drugs of abuse, such as opioids and amphetamines, represents nowadays a serious global problem which has economical, psychological, social and medical impact. Investigation of drug effects on the nervous system has been a subject of many studies during the last few decades. The interest in neurons regarding this issues is rather constant, but currently there is increasing number of studies focused on neuroglia and their role in drug addiction. Many studies demonstrated that glia are not only a part of neuropile and do not have only supporting function, but they play an important role in communication between neurons, participate in modulation of neurotransmission and could produce factors such as cytokines and chemokines. However, there is a not much information about the effect of drugs of abuse on neuroglia and the presumed role of these cells in the development of addiction in not quite clear. This review aims to provide a brief survey of current knowledge on this topic.

Key words: drugs of abuse, addiction, opioids, amphetamines, opioid receptors, neuroglia

2. Abstrakt

Drogy ako opioidy a amfetamíny predstavujú v súčastnosti celosvetový problém, ktorý má ekonomický, psychologický, sociálny a medicínsky dosah. Skúmanie účinkov drôg na nervový systém sa stal predmetom mnohých štúdií posledných desaťročí. Záujem o výskum neurónov v súvislosti s touto problematikou je konštantný, avšak v súčasnej dobe sa zvyšuje počet štúdií, ktoré sa zameriavajú na výskum neuroglií a ich úlohy pri drogových závislostí. Mnoho výskumov ukazuje, že že glie nie sú len súčasťou neuropilu a nemajú len podpornú funkciu, avšak hrajú významnú úlohu v komunikácii medzi neurónmi, podieľajú sa na modulácii nervového prenosu a dokážu produkovať pôsobky ako cytokíny a chemokíny. Avšak, nie je mnoho informácií o účinkoch drôg na neuroglie a ich predpokladaná úloha v rozvoji závislosti nie je úplne jasná. Táto štúdia má za cieľ poskytnúť stručný prehľad poznatkov o tejto téme.

Kľúčové slová: drogy, drogová závislosť, opioidy, amfetaminy, opioidné receptory, neuroglie

3. List of abbreviations

ACM - astrocyte conditioned medium

AMP - adenosine monophosphate

AMPA - alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

ATP - adenosine triphosphate

ATS - amphetamine type stimulants

BDNF - brain-derived neurotrophic factor

bFGF - basic fibroblast growth factor

cAMP - cyclic adenosine monophosphate

CD - cluster of differentiation

CeA - central nucleus of amygdala

CCL - CC chemokine ligand

CNS - central nervous system

CREB - cAMP-element binding protein

EAAT - excitatory amino acid transporters

Fos - FBJ murine osteosarcoma viral oncogene homolog

fra- FOS-like antigen

GABA - gamma-aminobutyric acid

GDNF - glial-derived neutotrophic factor

GFAP - glial fibrillary acidic protein

GLAST - L-glutamate/L-aspartate transporter

GLT - glutamate transporter

GTPase - guanosine triphosphatase

HSP - heat shock protein

IL- interleukin

LPS - lipopolysacharide

LTP - long-term potentiation

MAPK - mitogen activated protein kinase

MD - co-myeloid differentiation

mRNA - messenger ribonucleic acid

MS-153 - (R)-(-)-5-methyl-1-nicotinoyl-2-pyrazoline

NAcc - nucleus accumbens

NFkB - nuclear factor kappa B

NMDA - N-Methyl-D-aspartate

NO - nitric oxid

PDE - phosphodiesterase

PAK - protein kinase A

PNS - peripheral nervous system

PPF - propentophylin

TLR - toll-like receptor

4. Introduction

This review is focused on drugs of the group of opioids but, to a lesser extent, some attention is devoted also to amphetamine-type stimulants and cocaine and their effects on neuroglia. Opioids, mainly morphine, have been used for relieving pain for a long time. Their effects have been known since an ancient period. Except of their medical effects, opioids and their semi-synthetically/synthetically created chemical analogues can be unfortunately abused as psychoactive substances. Heroin is one of the most abused drugs of this type. According to WHO data, 230 million people used drugs at least once in 2010. There are about 27 million drug users what is 0.6 percent of adult population (UNODC, 2012). Heroin, cocaine and other drugs kill about 0.2 million people each year. Global opium production is amounted to 7000 tons in 2011. Opioids continue to be a dominant drug type in Asia, Europe, North America and Oceania according to treatment demand. Amphetamine-type stimulants are dominant in Asia. The main problems related to use of drugs are tolerance, withdrawal and hyperalgesia.

The fast development of science and technology allows to research in great detail molecular structures on the level of different proteins, receptors or DNA. Thanks to this, we have an opportunity to examine the effect different substances on organisms on the molecular level. Hughes et al. (1975) was one of the first, who isolated endogenous compounds binding to opioid receptors. Some organisms may produce endogenous opioids as a result of pain, reward or addiction. It is known that endogenous opioids affect the function of opioid receptors, which are highly abundant especially in the central nervous system. These receptors do not recognize only the opioids produced by own body but also react with appropriate substances from the outside. Opioid receptors have been found not only in the plasma membrane of neurons, but they are distributed also in glia.

There numerous studies dealing with the effects of drugs on neurons. A few years ago scientists started to focus on glia cells, too. It was found that glia cells are not only supportive cells in the CNS and PNS but also play a role in communication between neurons, modulation of neurotransmission and production of factors such as cytokines and chemokines.

There is still an open question about the role and possible participation of glia in the consequences of drug abuse.

5. Basic information on addictive drugs

5.1 Opioids

Morphine, a typical representative of opioids, is an opioid analgesic drug and the main psychoactive chemical of opium. Opium is dried latex which is obtained from *Papaver somniferum*. From poppy seed it is isolated by Sertürner' method. A wide range of semi-synthetic alkaloids created by simple chemical manipulations is very useful for medicine.

Opioids can be divided into four groups, according to Drug Reinforcement Agency (Trescot et al., 2008):

1) **Phenantrenes** are prototypical opioids. 6-hydroxyl group in the structure of these molecules may corfer a higher incidence of nausea and hallucinations. Opioids contained into this group are as follows: morphine, codeine, hydromorphone, levopranol, oxycodone, hydrocodone, oxymorphone, buprenorphine, nalbuphine and butorphanol.
2) **Benozonorphans** with one member of this class: pentazocine. It is agonist/antagonist with a high incidence of dysphoria.
3) **Phenylpiperidines:** a member of this group fentanyl has the highest affinity for the mu-opioid receptor. Opioids in this group are fentanyl, affentanil, sufentanil, and meperidine.
4) **Diphenylheptanes:** propoxyphene and methadone.

Tramadol does not belong to any above mentioned groups of opioids. It is an atypical opioid, a 4-phenyl-piperidine analogue of codeine, with partial mu agonist activity in CNS. These effects are related to GABA, catecholamine and serotonergic activity in addiction.

5.2 Amphetamine-type stimulants

Methamphetamine and amphetamine are synthetic substances which do not occur in nature. Methamphetamine is amphetamine with one additional methyl group on the chain. Amphetamine-type stimulants (ATS) are structurally similar to noradrenaline and dopamine and are able to inhibit dopamine metabolism and its reuptake and increase the release noradrenaline and serotonin (Berridge et al., 2002; Kuczenski et al., 1995). The monoaminergic system increases after a dose of amphetamine. ATS cause enhancement of dopamine release from nerve terminals (Kogeles et al., 1999; Silvia et al.,1997).

5.3 Cocaine

Cocaine is an alkaloid from *Erythroxylon coca* and it is the only naturally existing local anaesthetic. Cocaine enhances the activity of dopamine by blocking its reuptake (Silvia et al.,

1997; Volkow et al., 2000). According to Rasmussen et al., 2001; Ritz et al., 1990). Cocaine can also block reuptake of noradrenaline and serotonin and may increase noradrenaline release (Tuncel et al., 2002).

6. Basic concepts of drug addiction

Tolerance, sensitization and dependence are associated with chronic drug addiction. Drugs of abuse target neutral processes which are involved in reward-based learning (Hyman et al., 2006; Kalivas et al., 2008; Milton et al., 2010). Brain circuitry is the network of interconnected neurone throuhg which the electrical and chemical signals travel. Drugs of abuse afflict neurons interconnected in brain structures involved in reward-base learning. Nucleus accumbens, a region in the basal forebrain rostral to the preoptic area of the hypothalamus, is one of the most important structures implicated in drug addiction which play a role in psychological reward associated with addiction: learning, liking and wanting (Berridge et al., 2009). The NAcc and the olfactory tubercle form the ventral striatum, the part of basal ganglia. Dopamine activity in the NAcc does not habituate to repeat drug exposure by reduction of dopamine activity as it does after encounter with natural rewards (Wise et al., 1995; Hemby et al., 1997). According to Cadoni et al. (1999 and 2000) repeated drug exposure induces sensitization of dopaminergic transmission in the NAcc core. Chronic drug-induced dopamine stimulation may patologically strengthen the learning of stimuli related to drug availability via Pavlovian conditioning and the core with senzitized to dopamine transmission will start behavioral activity to obtain drug reward. Dopamine stimulation is connected to euphoric temper and satisfaction.

6.1. Tolerance, hyperalgesia and withdrawal

6.1.1 Tolerance to opioid analgesia

Opioid tolerance arises from repeated exposure to opioids and it is the manifestation of decreasing therapeutic effect and requirement for higher dose to maintain the same effect. According to Toda et al. (2009) three are specific signalling pathways involved in this process and according to Christie (2008) pharmacodynamic tolerance includes the following changes at different levels:

1) mu-opioid receptor: loss of intracellular signalling pathway capacity due to decreased expression and/or reduced coupling efficacy
2) homeostatic adaptation of the intracellular signalling system: increased cAMP level

3) at the system: adaptation to a network not related to mu-opioid receptor such as ORL1, choleocystokinin, NK1 signalling.

6.1.2 Hyperalgesia and allodynia

Allodynia is a pain caused by stimuli (temperature, physical stimuli) which normally do not provoke pain. By contrast, hyperalgesia is a massive exaggerated reaction on stimuli which are normally painful.

Opioid-induced hyperalgesia and opioid withdrawal-induced hyperalgesia have been shown to increase pain sensitivity. The studies of Dourish et al. (1988), Xu et al. (1992) and Vanderah et al. (2000,2001) claim that opioid-induced hyperalgesia is a result of increasing amounts of excitatory neurotransmitters such as choleocystokinin, which activates production of spinal dynorphins. Dynorphins are class of the opioid peptides from the precursor protein prodynorphin. Proprotein convertase 2 cleaves prodynorphine, which causes release of peptides such as: dynorphin A, dynorphin B, alpha/beta-neo-endomorphines. These peptides are involved in pain response (Han et al., 1984).

6.1.3. Withdrawal

The studies of Wang et al. (1997) and Volkow et al. (2007), and Martinez et al. (2004, 2005) have shown that withdrawal is associated with hypofunction in dopamine pathways, which is underlain by reduction of D2 receptor expression and dopamine release. Diminution of the dopaminergic system may contribute to anhedonia (decreased sensitivity to reward stimuli) and amotivation.

6.2. Neurocircuitry

The neurocircuitry (Fig. 1 and 2) forms the neuroplasticity associated with the development of drug abuse. Five circuits are involed in addiction: (1) the mesolimbic dopamine system, (2) the ventral striatum, (3) the ventral striatum/dorsal striatum/thalamus circuits, (4) the dorsolateral frotal cortex/inferior frontal cortex/hippocampus circuits, (5) the amygdala.

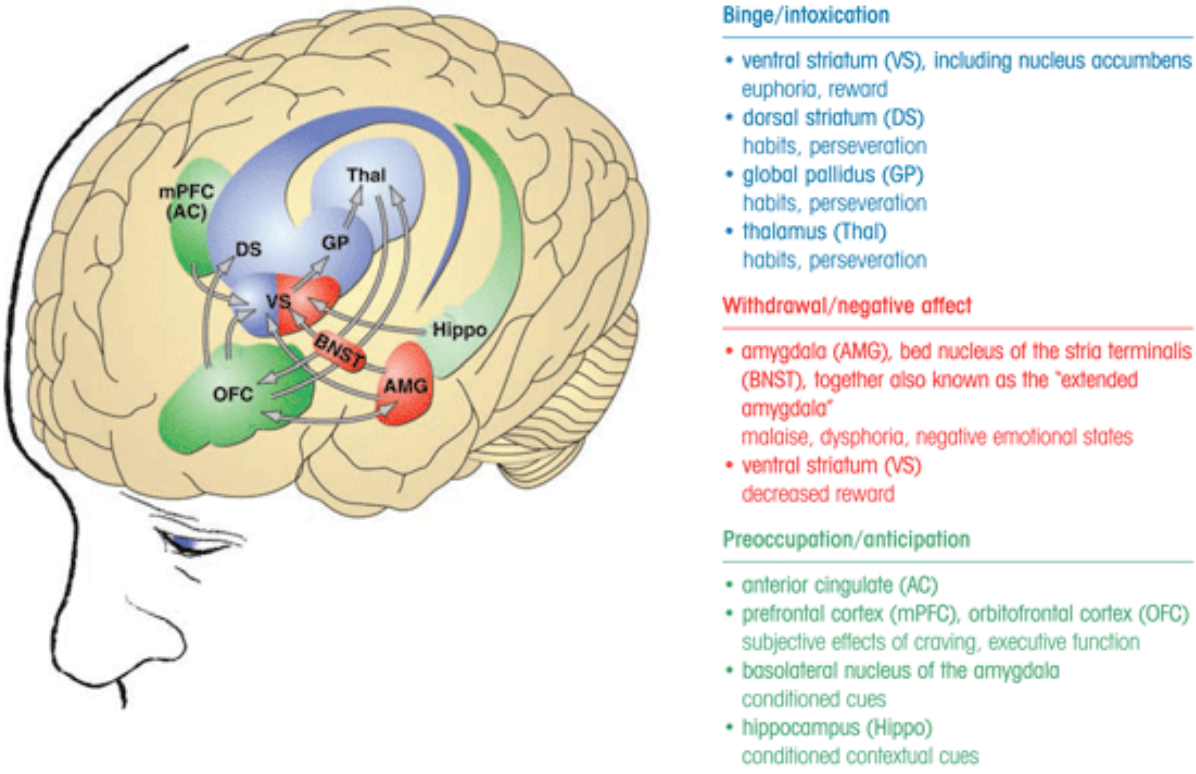

Fig. 1. Neurocircuitry. Adopted from Koob et al. (2008).

Glutamate is the main excitatory transmitter in the brain, which is involved in different brain function such as cognition, memory and learning. There are four types of glutamate receptors: NMDA, AMPA, delta and kainate receptors (summarized in Traynelis et al., 2010). All these receptors are nonselective cation channels, allowing the passage of Na^+ and K^+ and in come cases Ca^{2+} ions through the plasma membrane. Long-term potentiation (LTP) is a long-lasting increasing in signal transmission between two neurons which are stimulated at the same time (Cooke et al., 2006). It is one of the substantial mechanisms of synaptic plasticity whereby chemical synapses are able to change their strength. LTP is one of the major cellular mechanisms that are involved in learning and memory. It has been observed that *in vivo* exposure to morphine and nicotine induced LTP to AMPA-mediated neurotransmission in dopaminergic neurons (Saal et al., 2003). Not only morphine and nicotine but also amphetamine and cocaine can induce this effect (Sun et al., 2005). Interestingly, LTP lasting more than three months of abstinence was demonstrated in rats

(Chen et al., 2008). According to the study of Pierce et al. (1996) chronic cocaine exposure of rats elevated glutamate neurotransmission and these animals showed behavioral sensitization. Glutamatergic activity in NAcc slices strengthens LTP (Yao et al., 2004). Studies of Bondreau et al. (2005) and Conrad et al. (2008) demonstrated that three weeks of cocaine exposure increase the ratio of glutamate-1 receptors (GluR1) and on neurons which have low number of GluR2 was observed a slow redistribution of AMPA receptors. According to study of Chao et al. (2002), the expression of AMPA receptors depends on activation of dopamine D1 receptors and protein kinase A signalling. In study of Sutton et al. (2003) overexpression of GluR1 in the NAc relieved extinction of cocaine-seeking answers and increased threshold of reward. These changes resulted in (1) decreased reward and (2) lack of motivation (Todtenkopf et al., 2006). According to Nelson et al. (2009) the increase of AMPA expression does not occur in the amphetamine-sensitized rat. These observations led to a hypothesis of different functional effects of glutamate projections (Nelson et al., 2009).

Chronic cocaine administration inhibits basal release of glutamate but sensitizes synaptic glutamate release during restitution of obliterate of extinguished drug-seeking in rats (Kalivas et al, 2008; McFarland et al., 2003). Dysregulation of the cystine-glutamate exchange is another molecular target for regulation of the plasticity. According to study of Baker et al. (2003), chronic exposure to cocaine slows down cystine-glutamate exchange, leading to reduced basal and increased drug-induced glutamate in the NAcc. Cystin-glutamate exchanger controls the extracellular glutamate concentration. According to study of Kalivas (2004), lower basal levels of glutamate combined with elevation of synaptic glutamate from the prefrontal cortex afferens to the NAcc are the result of engaging in drug-seeking.

Long-lasting synaptic effects are characterized by (1) a decrease of glutamatergic neurotransmission during chronic exposure to the drug and (2) a persistent increase in the effectiveness of glutamatergic synaptic neurotransmission during recovery following withdrawal. These alternations promote excitation of the cells and are the base of drug-related learning in the addictive state (reviewed by Kauer et al., 2007).

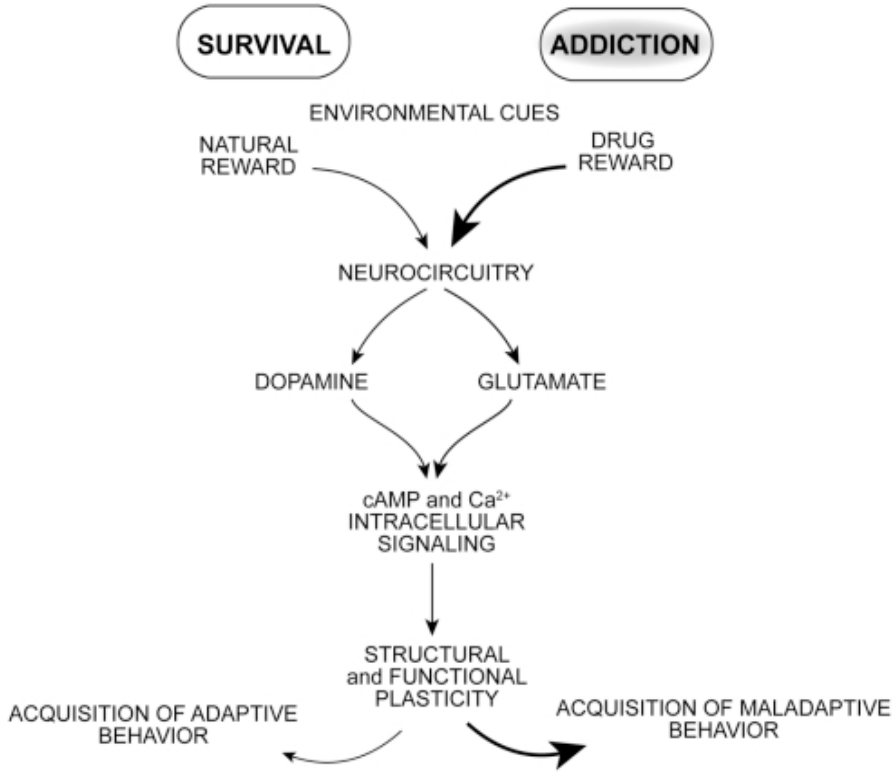

Fig. 2. Outline of neurocircitry of reward (natural and drug) on the level of receptors and their releasing factors. For more information see text above. Adopted from Philibin et al. (2011).

6.3. Molecular pathways of neuroplasticity

Molecular pathways involbed in natural and drug reward are summarised in Fig. 2 and 3. According to study of Edwards et al. (2007), chronic administration of opiates and cocaine leads to activation of cAMP-element binding protein (CREB) in the NAcc and CeA. CREB is a cellular transcription factor which is phosphorylated by protein kinase A (PKA). PKA regulates growth factors. PKA is setting in a point of convergence for some intracellular messenger pathway, which regulates gene expression. In study of Olson (2005) activation of CREB in the NAcc was connected to motivational symptoms of psychostimulant withdrawal. This process could be caused by induction of the dynorphin, which is opioid peptide that binds to kappa-opioid receptors and may be involved in the mechanism of depence and tolerance. Recurring CREB activation can support dynorphin expression in the NAcc which in turn inhibits dopaminergic activity. This modulation of dopaminergic signaling may cause negative emotional states.

Different transcription factors can be activated by CREB and other intracellular messengers. This activation leads to long-term changes in protein expression and as a result, neuronal function. According to study of Olson (2005), acute administration of drugs of abuse causes activation of the elements of the Fos protein family such as c-fos, FosB, Fra-1 and Fra-2 in the NAcc. In a longer period of time (days) also other transcription factors are activated, such as deltaFosB, which are a highly stable form of FosB. Activated dFosB may increase sensitivity to the rewarding effects of drugs of abuse (reviewed by McClung et al., 2004)

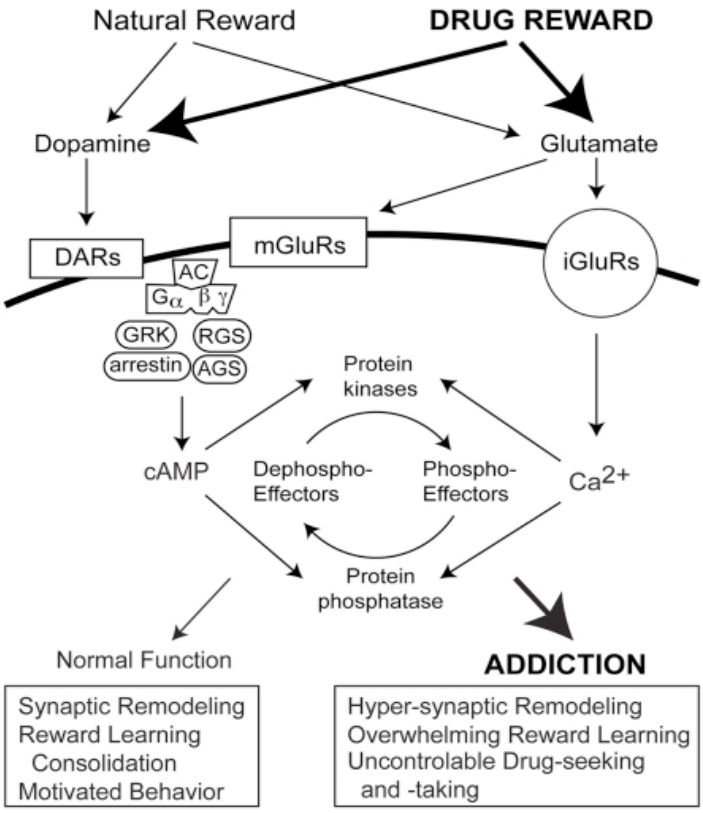

Fig. 3. Outline the molecular pathway of natural and drug reward. See text above. Adopted from Philibin et al. (2011).

Summary of changes in gene expression after long-term administration of drugs:

1) signal transduction in kappa opioid receptors (Fan et al., 2002; Kaewsuk et al., 2001; Przewlocka et al; 1994)
2) calcium binding proteins (Tirumalai and Howels, 1994)
3) transcription factors (Erdtmann-Vourliotis et al., 1998; Kelz et al., 1999)

7. Receptors

7.1 Opioid receptors

There is four types of opioid receptors: mu, delta, kappa and ORL1. ORL1 is genetically closely related to others. Activated opioid receptors tranduce signals through their cognate heterotrimeric G-proteins (Fig. 4.). All opioid receptors are 7-transmembrane spanning proteins that are connected to the inhibitory G-proteins. According to Childers et al. (1978), Galpha and Gbetagama subunits of G-proteins dissociate from one another after stimulation and act on intracellular effector pathways. It was found that GTPase activity of the G-protein alpha subunit is stimulated by endogenous opioid peptides or opioid agonists (Barchfeld et al., 1984). Stimulation of opioid receptors also inhibits cAMP production (Minneman et al., 1976). There is the inhibitory function on cAMP signalling which is Galpha dependent (Hsia et al., 1984; Taussig et al., 1993). Opioid receptors are also able to modulate calcium and potassium ion channels. In study of Rusin et al. (1997), opioid agonists caused a decrease in Ca^{2+} because they reduced P/Q-type, N-type and L-type currents. This effect was a result of binding of the dissociated Gbetagamma subunits directly to these ion channels and reduction in voltage activation of opening the pore (Zamponi et al., 2002, 1998)

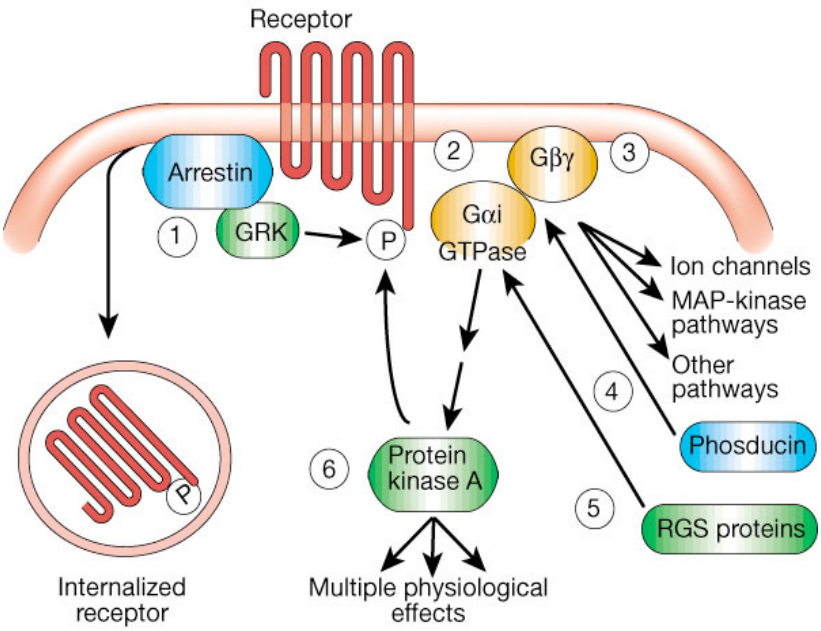

Fig. 4. Opioid receptor signalling pathway. Adopted from Nestler et al. (2001).

According to Sibinga and Goldstein (1988), interaction of opioids with opioids receptors can be characterized as follows:

1) opioid ligand needs an intact NH_2 terminus of the receptor
2) in the presence of GTP or increased concentration of sodium ion, opioid agonist binding is reduced; on the other hand, there is a minimal effect on an antagonist activity
3) binding to an opioid receptor is often of high afinity and stereoselective
4) binding is blocked by opioid antagonist such as naloxone
5) novel sites binding has similar afinity with previous opioids receptors
6) responses are pertussis-toxin sensitive involving receptor coupling to a G-protein

7.2 Opioid receptors in glial cells

Distribution of opioid receptors in astrocytes was determined in the following studies:

1) mu-opioid receptor (Dobrenis et al., 1995; Hauser et al., 1996; Ruzicka et al., 1996; Festa et al., 2002)
2) kappa-opioid receptor (Bunn et al., 1985; Maderspach et al., 1995)
3) delta-opioid receptor (Thorlin et al., 1998).

There is a lower level of mu-receptor mRNA, as compares with kappa- and delta-opioid receptors, in cortical, striatal, cerebellar, hippocampal and hypothalamic astrocytes (Ruzicka et al., 1995). The level of mRNA expression of opioid receptors in different astrocyte cultures is in the following order: cortex > hypothalamus > cerebellum + hippocampus > striatum (Ruzicka et al., 1995).

Mu-opioid receptor occurs in the spinal cord (Cheng et al., 1997), nucleus tractus solitarius (Glass et al., 2002), dentate gyrus (Drake et al., 2002), caudate putamen (Rodriguez et al., 2001) and nucleus accumbens. In the posterior pituitary was observed the greatest expression of kappa-opioid receptor (Bunn et al., 1985; Burnard et al., 1991). Microglia also express opioid receptors according to study of Horvath et al. (2010). Oligodendrocytes also express mu-opioid receptor (Knapp and Hauser, 1996; Knapp et al., 1998; Tryoen-Toth et al., 2000) and kappa-opioid receptor (Tryoen-Toth et al., 1998). According to study of Knapp et al. (1998), delta-opioid receptor expression does not take place in this cell.

7.3 TLR4

TLR4 is a receptor which detects lipopolysacharide (LPS) from Gram-negative bacteria and its role is the activation of the innate immune system. Interestingly, morphine can bind directly to TLR4 and its effect is associated with exaggerated response mediated via TLR4 and microglial activation after this drug administration in adolescence. The increased responsiveness could increase risk of drug-induced reinstatement in adulthood (Schwarz et al., 2013). These effects of morphine on microglia were studied in the region of the NAcc.

Opioid-induced glia activation increases tolerance, dependence, reward and breathing decrease. Intriguingly, these effects are apparently not the result of activation of opioid receptors, but TLR4, which is also at the same time the main glial receptor which participates in neuropathic pain (Watkins et al., 2009).

7.3.1 TL4 Glial activator receptor

TLR4 is mainly expressed by microglia, however, it can be found also in astrocytes, especially under neuroinflammatory conditions (Hutchinson et al., 2008). This receptor appears to be a major glial activator at the beginning of and during neuropathic pain. Although the TLR2 and TLR3 receptors are involved in neuropathic pain, most studies have been done just for the TLR4 receptor. There are several studies dealing with TLR2 (Mallard et al., 2009; Hong et al., 2010) and TLR3 (Obata et al., 2008).

7.3.2 TLR4 signalling

TLR4 signalling is active in a number of cellular cascades. It has been reported that LPS, which is agonist of TLR4 receptor, after interaction with LPS-binding protein is transferred to CD14 co-receptor on the cell membrane (Laird, 2009). This leads to intracellular activation of acid sphingomyelinase, which generates ceramide. Subsequently, lipid rafts are formed containing MD2, which is co-myeloid differentiation factor receptor, interacting with TLR4, HSP 70, 90 and others. CD14 brings LPS to the vicinity of MD2 and interaction of these proteins results in heterodimerization and subsequently to homodimerization of MD2-TLR4 (Fig. 5.). The following intracellular signalling steps occur through at least three parallel paths. The first two, cell movement and cell survival/apoptosis are mediated via the PI3K/Akt. The third one, which leads to production of pro-inflammatory factors, is mediated via activation of NFkB and cytokines through the MAPK cascade. It is important to note that

(+)-naloxone, (-)-naltrexone and (+)-naltrexone causes the inhibition of TLR4 (Hutchinson et al., 2008).

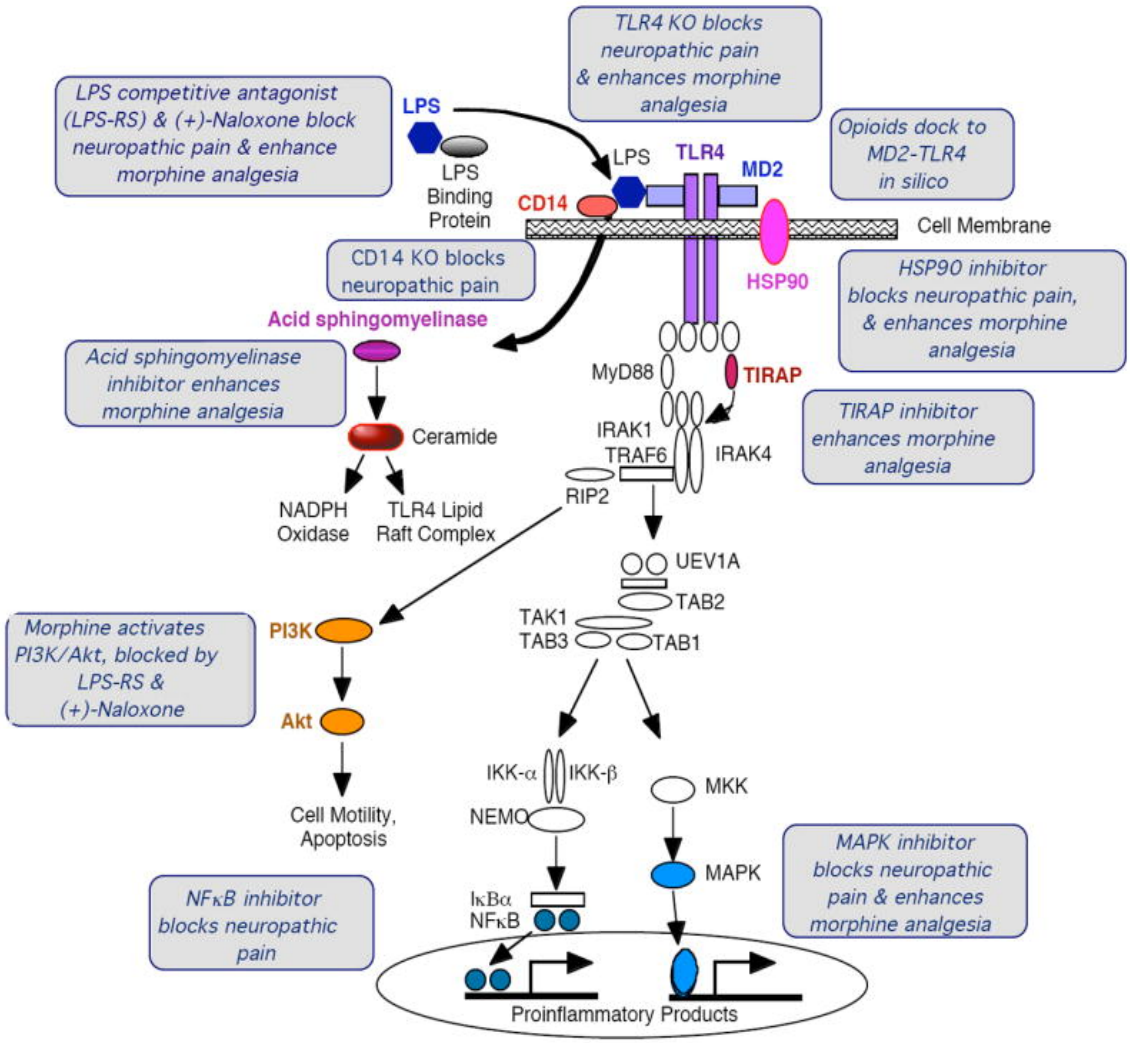

Fig. 5. TLR4: Glial activator receptor. Adopted from Watkins et al. (2009)

8. Neuroglia

Neuroglia are cells in the central and peripheral nervous system which play a crucial role in maintenance and protection of neurons. These cells participate in nutrient supply, defensive actions and myelinization and they are part of neuropile. These cells are not only supporting

cells in the central and peripheral nervous system, but also play a crucial role in communication, modification of neuron's answer and releasing factors such as cytokines and chemokines.

Glia cells are divided according to their morphological and functional characteristics. According to morphological differences these cells are divided into two groups: microglia and macroglia (astrocytes and oligodendrocytes in this study).

Studies dealing with the effects of drugs on glial cells were conducted mainly on astrocytes, microglia and oligodendrocytes. There are several *in vitro* studies that revealed a direct action of opioids on glia (Hutchinson et al., 2008; Narita et al., 2006; Horvath et al., 2009; Takayama et al., 2005). According to works of Hutchinson et al. (2008) and Tawfik et al. (2005), opioids activate glial cells and this activation leads to release of pro-inflammatory products, including cytokines. Hauser (1996) and Merrill and Benveniste (1996) reported that a lot of neuronal signals such as ATP, NO, substation P, excitatory amino acids or proinflammatory cytokines can also stimulate glia.

Under *in vivo* conditions, activation of glia by drugs could happen via microglial or astrocytic activation markers, which are induced by morphine (Cui et al., 2006, Hutchinson et al., 2009). Activation of glia by drugs could block the pro-inflammatory cytokines which increase the morphine analgesia (Hutchinson et al., 2008; Shavit et al., 2005). According to study of Cui et al. (2006), selective activation of microglial p38 MAPK is induced by opioids and inhibition of p38 MAPK attenuates tolerance to morphine algesia.

8.1 Astrocytes

These cells were introduced by Michael von Lenhossek in 1891 (Parpura et al., 2012). Besides others, the role of astrocytes is delivery of nutrients and neurotransmitter precursors and regulation of cerebral blood flow. According to Smith (2010), astrocyte may have about 30,000 connections with adjacent cells. These connections provide integrating and modulatory capability. Astrocytes can regulate nervous transmission in the following ways:

1) by releasing of neurotransmitters (Fellin and Carmignoto, 2004)
2) by neurotrophic factors (Brenneman et al., 1997)
3) by cytokines and chemokines (Dong and Benveniste, 2001)
4) by formation of extracellular matrix (Brightman, 2002).

Astrocytes are distributed in all parts of the CNS and they have a lot of different functions, such as participation in constitution of the brain-blood barrier or formation of a tripartite

synapse (Araque et al., 1999). The tripartite synapse (Fig. 6) is a concept of existence of bidirectional interactions between astrocytes and neurons, whereby astrocytes may modulate communication between presynaptic and postsynaptic neuron. This modulation reflects active participation of astrocytes in a synaptic function.

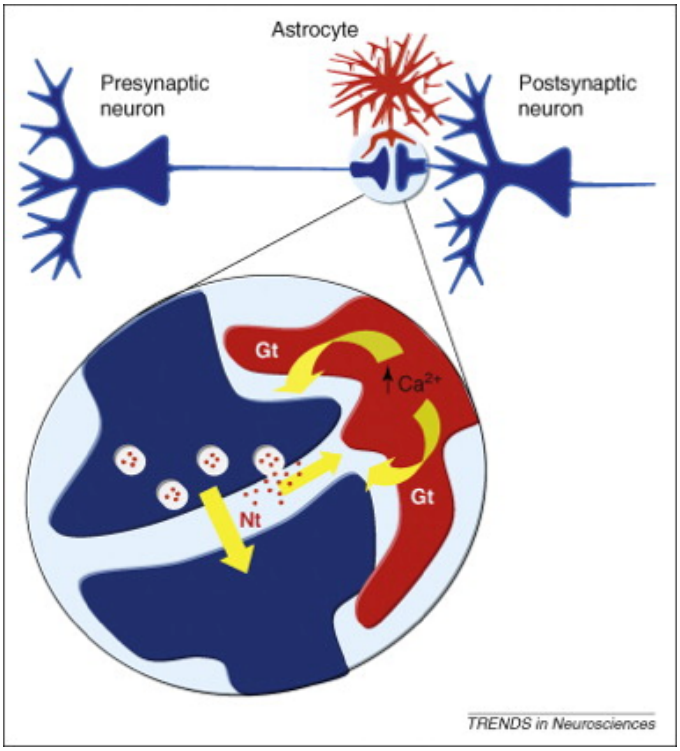

Fig. 6. Tripartite synapse: the transmission of information between a presynaptic and postsynaptic neuron and astrocyte. Adopted from Araque et al. (1999).

In addiction the role of astrocytes is in maintenance of glutamate homeostasis, which has an important role in the synaptic activity, and high doses of extracellular glutamate may cause influx of calcium ions into the neurons and result in uncontrolled signaling and neurotoxicity. There are two main types of glutamate transporters: EAAT1 (rat homolog glutamate/aspartate transporter GLAST) and EAAT2 (rat homolog glutamate transporter -1, GLT-1) (Hertz et al., 2004). These transporters are primarily expressed in astrocytes but they are also in other neuroglia in a limited extent. According to studies of Hyman et al. (2005) and Kalivas (2004), the glutamatergic system is involved in the process of learning which leads to behavior during addiction. Glutamate transport activator MS-153, when applied along with morphine, methamphetamine, or also cocaine, could significantly reduce place preference without subsequent locomotor responses (Nakagawa et al., 2005). This compound was also able to

reduce the development of morphine tolerance and physical addiction when applied along with morphine (Nakagawa et al., 2001).

To determine the role of astrocytes, astrocyte conditioned medium (ACM) was used in experiments of Narita et al. (2006). ACM is used to support growth of neurons and endothelial cells and in this study it was applied for investigation how astrocyte-related soluble factors are involved in the development of rewarding effects induced by drugs of abuse. Application of ACM into the NAcc of a mouse after administration of methamphetamine or morphine in a dose which causes addiction increased rewarding effects of these drugs by the way of activation of the Janus kinase signal transducers and activators of transcription (Jak/STAT) pathway, which modulates astrogliosis and astrogliogenesis.

8.1.1. GFAP

GFAP protein is the main protein of intermediate filaments of glial cells in differential fibrous and protoplasmatic astrocytes in the CNS. GFAP is part of cytoskeleton and is important for keeping the cell shape. Astrocytes in drug addicts show elongated fiber structures which contain a significant amount of GFAP in comparison with control samples. The changes are prominent in hippocampal astrocytes (Weber et al., 2013). Interestingly, brain injury and neurotoxicity is also accompanied by increased levels of GFAP (Hill et al., 1996). A long-term therapy with morphine increases the expression of GFAP and enlargement of astrocytes in the ventral segmental area, frontal cortex, NAcc, locus coeruleus and nucleus of the solitary tracts in rats (Marie-Claire, et al., 2004; Beitner-Johnson et al., 1993; Song et al., 2001; Garrido et al, 2005; Alonso et al., 2007). Methamphetamine reduces dopaminergic terminals without loss of neurons (Ricaurte et al., 1984), but induces astrogliosis with increasing of GFAP in the frontal cortex, striatum and hipocampus (Pubill et al., 2003).

It was observed that astrocytes inactivation by the gliotoxin fluorocitrate inhibits morphine-induced increasing of GFAP, toleration and morphine analgesia (Song et al., 2001). MDMA (Ecstasy) is an exception in comparison to other stimulants, because it does not increase GFAP expression or activation of microglia, although it causes reduction of dopaminergic and serotonergic terminals (Pubill et al., 2003).

Narita et al. (2006) reported that *in vitro* treatment of a mouse neural/glial cells in culture with methamphetamine (10 uM) or morphine (10 uM) during the period of three days caused activation of astrocytes and at the same time increased the level of GFAP and did not cause the death of neurons. Similar results were obtained in subsequent experiments of the

same group (Narita et al., 2005). On the other hand, morphine (10 uM) but not methamphetamine (10 uM) induced activation of cortical astrocytes.

Propentophylline is a xantine derivate known for its neuroprotective effects and it has been shown to modulate a glial activity under pathological conditions when astrocytes are activated by methamphetamine and morphine (Sweitzer et al., 2001; Rhagavendra et al., 2004). Amphetamine may cause reduction in striatal neuroglia and gliogenesis in the subventricular zone and the somatosensory cortex *in vivo*. Liu et al. (2013) reported changes in GFAP mRNA copy numbers using quantitative RT-PCR in these regions after amphetamine administration.

8.1.2. GDNF

The neurotrophic activity of astrocytes can participate in the effects of cocaine in the ventral tegmental area. Glia-derived neurotrophic factor (GDNF) is mainly in astrocytes, but it is produced in microglia, too (Appel et al., 1997; Chang et al., 2006). GDNF supports survival and differentiation of dopaminergic neurons and protects these cells from methamphetamine-induced neurotoxicity in mice (Cass, 1996). As observed in study of Pierce et al. (2001), after administration of GDNF into the VTA a significant reduction occured in the increase of a key protein, neurotrophin, induced by exposure to cocaine.

8.1.3. BDNF

BDNF produced mostly by astrocytes plays a role as a factor of survival for some neurons and it participates in synaptic plasticity in the cortex and other subcortical. The BDNF signaling pathway, which starts from non-noradrenergic sources such astrocytes, is essential for opioid induced adaptation of the noradrenergic system (Akbarian et al., 2002). This factor can also be involved in response to withdrawal symptoms (Akbarian et al., 2001). The BDNF/TrkB pathway is implicated in the methamphetamine-induced release of dopamine (Narita et al., 2003).

8.1.4. bFGF

Astrocytes produce not only BDNF, but also bFGF, which plays a role in the development of sensitivity to amphetamines (Yamada et al., 2004). According to the study of Fumagalli et al. (2006), one dose of cocaine transiently increased the level of bFGF in the striatum and prefrontal cortex, but longer exposition resulted in continuously higher level bFGF in these brain regions.

8.2. Microglia

Microglia was discovered by Pio del Rio-Hortega in 1932 (summarized in Rezaie et al., 2002). These cells originate from monocytes and their role is phagocytosis in the CNS. Microglia respond to damage or stress situations in the CNS. Activation of microglia includes always proliferation of these cells or increase of expression of immunomolecules or changes of their function such as release of cytotoxic or/and inflammatory mediators.

Microglia, similarly to the other cells in the immune system, express opioid receptors (Bidlack, 2000; Chao et al., 1997). Hu et al. (2002) have shown that overstimulation of these receptors leads to apoptosis. Stimulation by morphine can stimulate phagocytosis (Peterson et al., 1995; Lipovsky et al., 1998) and decrease microglial chemotaxis via complement protein 5a (Chao et al., 1997) and CCL5 (Hu et al., 2000). On the other hand, study of Shanks et al. (2012) revealed that methamphetamine but not amphetamine can inhibit phagocytosis. According to De Leo (2006) microglia can modulate neuron response similarly to astrocytes. This concept is represented by a tetrapartite synapse (Fig. 7).

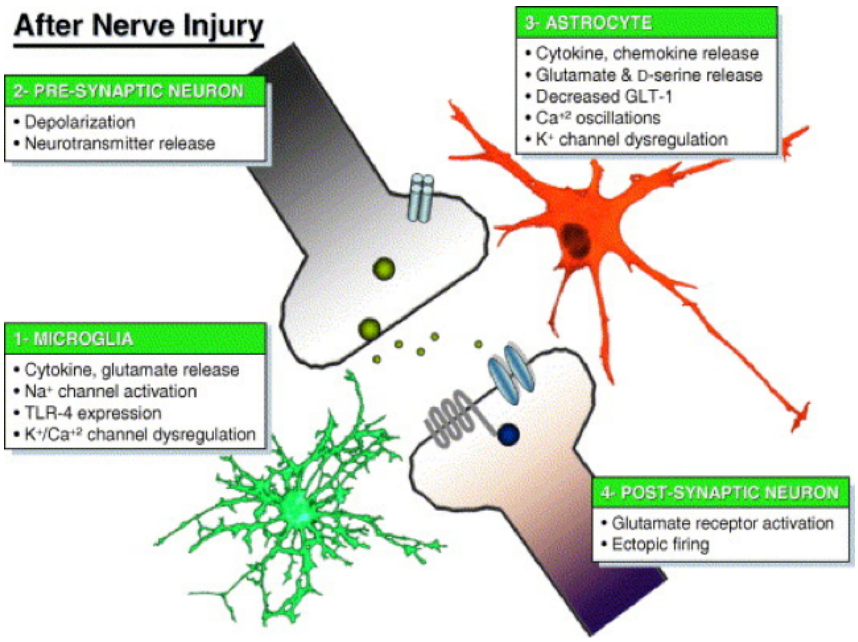

Fig. 7. Tetrapartite synaptic unit. Adopted from De Leo et al. (2006).

Below is summarized experimental evidence concerning microglia activation mechanisms after nerve injury, surgical procedures and chronic opioid exposure:

1) Phosphorylation of p38 through activation of P2X4 receptor and increased synthesis and release of the neurotrophin BDNF, which, among others, might increase neuropathic pain through the inhibition of synaptic transmission in the spinal cord (Wu et al., 2006).
2) At the same time, this phosphorylation increases the synthesis of pro-inflammatory cytokine IL-1b, IL-6, TNF-alpha and the transcription factor NF-kB (Haydon et al., 2009), LPS, which is a potential activator of microglia and TLR4 ligand, which indicates the release of other glia.
3) Increased IL-1b, IL-6 and TNF-a indicate the hyperactivity of neurons in the dorsal root of the rear corners. This condition leads to hypersensitivity (Hutchinson et al., 2007; Noman et al., 2009).
4) Intratecal administration of IL-1b, IL-6, TNF-a induces potent hyperalgesia and allodynia. CREB activates the same factors which are critical in transcription of pronociceptive genes such as neurokinin-1 and Cox-2 (Lewis et al., 2009).

In the study of Viviani et al. (2003), IL-1B increased NMDA conductance in neurons also in the spinal cord dorsal horn. According to study of Beattie et al. (2002), TNF-alpha significantly enhances membrane neuronal AMPA receptors and conductance. TNF-alpha also increases neuroexcitability in response to glutamate (Emch et al., 2001).

8.3. Oligodendrocytes

The role of oligodendrocytes is in maintenance and isolation of neuron axons in the CNS. The same role with some morphological differences is played by Swan's cells in the PNS. One oligodendrocyte may roll with myelin approximately 50 axons. Oligodendrocytes are not as well characterized as astrocytes or microglia cells as far as their role in drug addiction concerned. Bannon et al. (2005) and Albertson et al. (2004) have found using microarrays that the expression of mRNAs of many proteins is greatly reduced in patients addicted to cocaine. These proteins are involved in the process of myelination in the NAcc, which has been reduced to oligodendrocytes immunoreactive for myelin basic protein. At the moment there are no studies where the correlation between the change in behavior among drug addicts and function of oligodendrocytes in the NAcc, optionally in other relevant areas of the brain.

Oligodendrocytes, like other glial cells, are capable of producing neurotrophic factors in response to the surrounding neurons (Du et al., 2002).

9. Minocycline, fluorocitrat and ibudiblast (AV411)

These substances are in the center of interest of many scientists (Meller et al., 1994; Milligan et al., 2000 and 2003; Ragavendra et al., 2003; Ledeboer et al., 2005) because of their effects on neuroglia in pain control. Glial activation inhibitors such as fluorocitrat, minocycline and possibly ibudilast (AV411) increase the morphine analgesia (Hutchinson et al., 2008, Hutchinson et al., 2009; Cui et al., 2008). They can be important in prevention of hyperalgesia or relieving of symptoms associated with long-term use of drugs.

Fluorocitrate, a metabolite of fluoroacetate, according to study of Hassel et al. (1992) disrupts the Krebs cycle via inhibiting aconitase. Berg-Johnsen et al. (1993) observed that this compound causes reduction in the glial tricarboxylic acid cycle and accordingly in the level of glutamine, the main precursor of glutamate.

Minocycline, a broad-spectrum tetracyclic antibiotic, inhibits activation of microglia but, on the other hand, it does not exert any direct effect on neurons or astrocytes (Ledeboer et al., 2005) and stops locomotor activity induced by cocaine or methamphetamine in mice (Chen et al., 2009; Fujita et al., 2012).

Ibudilast (AV411), 3-isobutyryl-2-isopropylpyrazolo-[1,5-a]pyridine, was found to inhibit phosphodiesterase (PDE) and pro-inflammatory activity. In parallel, administration of AV411 blocked the response to methamphetamine exposure in rats (Snider et al., 2013; Beardsley et al., 2010). AV411 may decrease opioid dependence and withdrawal signs (Hutchinson et al., 2009; Ledeboer et al., 2007) and also attenuate morphine-induced release of dopamine in the NAcc (Bland et al., 2009).

10. Conclusions

Neuroglia are not only supportive cells in the CNS and PNS but also play a lot of other important roles. The substances such as drugs of abuse can activate these cells in a specific way. The studies dealing with the effects of drugs on glia have been mainly performed on on astrocytes, microglia and oligodendrocytes.

The best reviewed glia are astrocytes which after their activation are able to produce cytokines and chemokines (Achour and Pascual, 2010). According to Araque (1999) there is a concept of tripartite synapse, the concept of existence of both sides communication between

an astrocyte and presynaptic and postsynaptic neuron. As a result of this modulation there is an active participation of astrocyte in a synaptic function. In the study of Hertz et al., 2004, the role of astrocytes in addiction is the keeping of glutamate homeostasis, which has an important role in the synaptic activity. There is a direct evidence that among drug addicts the level of GFAP is higher (Weber et al., 2013; Marie-Claire et al., 2004; Beitner-Johnson et al., 1993; Song et al., 2001; Garrido et al., 2005; Alonso et al., 2007), also GDNF (Appel et al., 1997; Lee et al., 2006), BDNF (Akbarian et al., 2002, 2001), bFGF (Yamada et al., 2004; Fungamalli et al., 2006) in comparison with control samples.

Microglia, main cells of the immune system in the brain, are important for their role in phagocytosis (Peterson et al., 1995; Lipovsky et al., 1998) but they are involved in chemotaxis, too (Chao et al., 1997; Hu et al., 2000). According to De Leo (2006), microglia provide a modulation of neuron response similarly to astrocytes, and they are part of a tetrapartite synapse.

It has been demonstrated that glial cells after activation by opioids increase tolerance, dependence, reward and depress breathing. These effects depend mainly on TLR4 and less on opioid receptors (Watkins et al., 2009). TLR4 is the main glial receptor which participates in neutropathic pain.

Fewer studies have been devoted to oligodendrocytes. However, it has been found that many proteins expressed in these cells involved in the process of myelination are reduced in patients addicted to cocaine (Bannon et al., 2005; Albertson et al., (2004).

Promise for the future lies in the prevention of allodynia and hyperalgesia (Meller et al., 1997; Milligan et al., 2000 and 2003; Rhagavendra et al, 2003; Ledeboer et al., 2005) therefore substances like minocycline, which inhibits activation of microglia (Ledeboere et al., 2005), fluorocitrate, which inhibits activation of astrocytes (Hassel et al., 1992; Borg-Johnsen et al., 1993) or ibudilast (AV411), which inhibit phosphodiesterase (PDE) and pro-inflammatory activity. (Snider et al., 2013; Beardsley et al., 2010). However, more research focused on these substances is needed.

There is a number of studies dealing with consequences of drug administration in neurons but there are only few studies about the role of glia in the mechanism of tolerance, withdrawal and hyperalgesia. It is necessary to pay more attention to delineation of communication between glia and neurons, glial receptors, modulation of synaptic transmission, influence of opioid-induced releasing factors, and others.

Here are some topics possibly important for future research:

1) studies of oligodendrocytes, Swan cells and other types of glia and their modification after drug administration
2) investigation of the consequences of increased levels of GFAP, GDNF, BDNF, bFGF
3) possible use of minocycline, fluorocitrate and ibudilast (AV411) in a prevention of hyperalgesia and allodynia.

11. References

Akbarian, S., Bates, B., Liu, R. J., Skirboll, S. L., Pejchal, T., Coppola, V., Jaenisch, R. (2001). Neurotrophin-3 modulates noradrenergic neuron function and opiate withdrawal. *Mol Psychiatry, 6*(5), 593-604. doi: 10.1038/sj.mp.4000897

Akbarian, S., Rios, M., Liu, R. J., Gold, S. J., Fong, H. F., Zeiler, S., Jaenisch, R. (2002). Brain-derived neurotrophic factor is essential for opiate-induced plasticity of noradrenergic neurons. *J Neurosci, 22*(10), 4153-4162. doi: 20026381

Albertson, D. N., Pruetz, B., Schmidt, C. J., Kuhn, D. M., Kapatos, G., & Bannon, M. J. (2004). Gene expression profile of the nucleus accumbens of human cocaine abusers: evidence for dysregulation of myelin. *J Neurochem, 88*(5), 1211-1219.

Alonso, E., Garrido, E., Diez-Fernandez, C., Perez-Garcia, C., Herradon, G., Ezquerra, L., . . . Alguacil, L. F. (2007). Yohimbine prevents morphine-induced changes of glial fibrillary acidic protein in brainstem and alpha2-adrenoceptor gene expression in hippocampus. *Neurosci Lett, 412*(2), 163-167. doi: 10.1016/j.neulet.2006.11.002

Appel, N. M., Rapoport, S. I., & O'Callaghan, J. P. (1997). Sequelae of parenteral domoic acid administration in rats: comparison of effects on different anatomical markers in brain. *Synapse, 25*(4), 350-358. doi: 10.1002/(sici)1098-2396(199704)25:4<350::aid-syn6>3.0.co;2-9

Araque, A., Parpura, V., Sanzgiri, R. P., & Haydon, P. G. (1999). Tripartite synapses: glia, the unacknowledged partner. *Trends Neurosci, 22*(5), 208-215.

Baker, D. A., McFarland, K., Lake, R. W., Shen, H., Tang, X. C., Toda, S., & Kalivas, P. W. (2003). Neuroadaptations in cystine-glutamate exchange underlie cocaine relapse. *Nat Neurosci, 6*(7), 743-749. doi: 10.1038/nn1069

Bannon, M., Kapatos, G., & Albertson, D. (2005). Gene expression profiling in the brains of human cocaine abusers. *Addict Biol, 10*(1), 119-126. doi: 10.1080/13556210412331308921

Barchfeld, C. C., & Medzihradsky, F. (1984). Receptor-mediated stimulation of brain GTPase by opiates in normal and dependent rats. *Biochem Biophys Res Commun, 121*(2), 641-648.

Beardsley, P. M., Shelton, K. L., Hendrick, E., & Johnson, K. W. (2010). The glial cell modulator and phosphodiesterase inhibitor, AV411 (ibudilast), attenuates prime- and stress-induced methamphetamine relapse. *Eur J Pharmacol, 637*(1-3), 102-108. doi: 10.1016/j.ejphar.2010.04.010

Beattie, M. S., Ferguson, A. R., & Bresnahan, J. C. (2010). AMPA-receptor trafficking and injury-induced cell death. *Eur J Neurosci, 32*(2), 290-297. doi: 10.1111/j.1460-9568.2010.07343.x

Beitner-Johnson, D., Guitart, X., & Nestler, E. J. (1993). Glial fibrillary acidic protein and the mesolimbic dopamine system: regulation by chronic morphine and Lewis-Fischer strain differences in the rat ventral tegmental area. *J Neurochem, 61*(5), 1766-1773.

Berg-Johnsen, J., Paulsen, R. E., Fonnum, F., & Langmoen, I. A. (1993). Changes in evoked potentials and amino acid content during fluorocitrate action studied in rat hippocampal cortex. *Exp Brain Res, 96*(2), 241-246.

Berridge, C. W., & Stalnaker, T. A. (2002). Relationship between low-dose amphetamine-induced arousal and extracellular norepinephrine and dopamine levels within prefrontal cortex. *Synapse, 46*(3), 140-149. doi: 10.1002/syn.10131

Bidlack, J. M. (2000). Detection and function of opioid receptors on cells from the immune system. *Clin Diagn Lab Immunol, 7*(5), 719-723.

Bland, S. T., Hutchinson, M. R., Maier, S. F., Watkins, L. R., & Johnson, K. W. (2009). The glial activation inhibitor AV411 reduces morphine-induced nucleus accumbens dopamine release. *Brain Behav Immun, 23*(4), 492-497. doi: 10.1016/j.bbi.2009.01.014

Boudreau, A. C., & Wolf, M. E. (2005). Behavioral sensitization to cocaine is associated with increased AMPA receptor surface expression in the nucleus accumbens. *J Neurosci, 25*(40),

9144-9151. doi: 10.1523/jneurosci.2252-05.2005
Brenneman, D. E., Phillips, T. M., Festoff, B. W., & Gozes, I. (1997). Identity of neurotrophic molecules released from astroglia by vasoactive intestinal peptide. *Ann N Y Acad Sci, 814*, 167-173.
Brightman, M. W. (2002). The brain's interstitial clefts and their glial walls. *J Neurocytol, 31*(8-9), 595-603.
Bunn, S. J., Hanley, M. R., & Wilkin, G. P. (1985). Evidence for a kappa-opioid receptor on pituitary astrocytes: an autoradiographic study. *Neurosci Lett, 55*(3), 317-323.
Burbassi, S., Sengupta, R., & Meucci, O. (2010). Alterations of CXCR4 function in mu-opioid receptor-deficient glia. *Eur J Neurosci, 32*(8), 1278-1288. doi: 10.1111/j.1460-9568.2010.07402.x
Burnard, D. M., Pittman, Q. J., & Macvicar, B. A. (1991). Neurotransmitter-mediated changes in the electrophysiological properties of pituicytes. *J Neuroendocrinol, 3*(4), 433-439. doi: 10.1111/j.1365-2826.1991.tb00300.x
Cadoni, C., & Di Chiara, G. (1999). Reciprocal changes in dopamine responsiveness in the nucleus accumbens shell and core and in the dorsal caudate-putamen in rats sensitized to morphine. *Neuroscience, 90*(2), 447-455.
Cadoni, C., & Di Chiara, G. (1999). Reciprocal changes in dopamine responsiveness in the nucleus accumbens shell and core and in the dorsal caudate-putamen in rats sensitized to morphine. *Neuroscience, 90*(2), 447-455.
Cadoni, C., & Di Chiara, G. (2000). Differential changes in accumbens shell and core dopamine in behavioral sensitization to nicotine. *Eur J Pharmacol, 387*(3), R23-25.
Cadoni, C., Solinas, M., & Di Chiara, G. (2000). Psychostimulant sensitization: differential changes in accumbal shell and core dopamine. *Eur J Pharmacol, 388*(1), 69-76.
Cass, W. A. (1996). GDNF selectively protects dopamine neurons over serotonin neurons against the neurotoxic effects of methamphetamine. *J Neurosci, 16*(24), 8132-8139.
Chang, Y. P., Fang, K. M., Lee, T. I., & Tzeng, S. F. (2006). Regulation of microglial activities by glial cell line derived neurotrophic factor. *J Cell Biochem, 97*(3), 501-511. doi: 10.1002/jcb.20646
Chao, C. C., Hu, S., Shark, K. B., Sheng, W. S., Gekker, G., & Peterson, P. K. (1997). Activation of mu opioid receptors inhibits microglial cell chemotaxis. *J Pharmacol Exp Ther, 281*(2), 998-1004.
Chao, S. Z., Ariano, M. A., Peterson, D. A., & Wolf, M. E. (2002). D1 dopamine receptor stimulation increases GluR1 surface expression in nucleus accumbens neurons. *J Neurochem, 83*(3), 704-712.
Chen, B. T., Bowers, M. S., Martin, M., Hopf, F. W., Guillory, A. M., Carelli, R. M., . . . Bonci, A. (2008). Cocaine but not natural reward self-administration nor passive cocaine infusion produces persistent LTP in the VTA. *Neuron, 59*(2), 288-297. doi: 10.1016/j.neuron.2008.05.024
Chen, H., Uz, T., & Manev, H. (2009). Minocycline affects cocaine sensitization in mice. *Neurosci Lett, 452*(3), 258-261. doi: 10.1016/j.neulet.2009.01.078
Cheng, P. Y., Liu-Chen, L. Y., & Pickel, V. M. (1997). Dual ultrastructural immunocytochemical labeling of mu and delta opioid receptors in the superficial layers of the rat cervical spinal cord. *Brain Res, 778*(2), 367-380.
Childers, S. R., & Snyder, S. H. (1978). Guanine nucleotides differentiate agonist and antagonist interactions with opiate receptors. *Life Sci, 23*(7), 759-761.
Christie, M. J. (2008). Cellular neuroadaptations to chronic opioids: tolerance, withdrawal and addiction. *Br J Pharmacol, 154*(2), 384-396. doi: 10.1038/bjp.2008.100
Conrad, K. L., Tseng, K. Y., Uejima, J. L., Reimers, J. M., Heng, L. J., Shaham, Y., . . . Wolf, M. E. (2008). Formation of accumbens GluR2-lacking AMPA receptors mediates incubation of

cocaine craving. *Nature, 454*(7200), 118-121. doi: 10.1038/nature06995
Cooke, S. F., & Bliss, T. V. (2006). Plasticity in the human central nervous system. *Brain, 129*(Pt 7), 1659-1673. doi: 10.1093/brain/awl082
Cui, Y., Chen, Y., Zhi, J. L., Guo, R. X., Feng, J. Q., & Chen, P. X. (2006). Activation of p38 mitogen-activated protein kinase in spinal microglia mediates morphine antinociceptive tolerance. *Brain Res, 1069*(1), 235-243. doi: 10.1016/j.brainres.2005.11.066
Cui, Y., Liao, X. X., Liu, W., Guo, R. X., Wu, Z. Z., Zhao, C. M., . . . Feng, J. Q. (2008). A novel role of minocycline: attenuating morphine antinociceptive tolerance by inhibition of p38 MAPK in the activated spinal microglia. *Brain Behav Immun, 22*(1), 114-123. doi: 10.1016/j.bbi.2007.07.014
De Leo, J. A., Tawfik, V. L., & LaCroix-Fralish, M. L. (2006). The tetrapartite synapse: path to CNS sensitization and chronic pain. *Pain, 122*(1-2), 17-21. doi: 10.1016/j.pain.2006.02.034
Dobrenis, K., Makman, M. H., & Stefano, G. B. (1995). Occurrence of the opiate alkaloid-selective mu3 receptor in mammalian microglia, astrocytes and Kupffer cells. *Brain Res, 686*(2), 239-248.
Dong, Y., & Benveniste, E. N. (2001). Immune function of astrocytes. *Glia, 36*(2), 180-190.
Dourish, C. T., Hawley, D., & Iversen, S. D. (1988). Enhancement of morphine analgesia and prevention of morphine tolerance in the rat by the cholecystokinin antagonist L-364,718. *Eur J Pharmacol, 147*(3), 469-472.
Drake, C. T., Chang, P. C., Harris, J. A., & Milner, T. A. (2002). Neurons with mu opioid receptors interact indirectly with enkephalin-containing neurons in the rat dentate gyrus. *Exp Neurol, 176*(1), 254-261.
Du, Y., & Dreyfus, C. F. (2002). Oligodendrocytes as providers of growth factors. *J Neurosci Res, 68*(6), 647-654. doi: 10.1002/jnr.10245
Edwards, S., Graham, D. L., Bachtell, R. K., & Self, D. W. (2007). Region-specific tolerance to cocaine-regulated cAMP-dependent protein phosphorylation following chronic self-administration. *Eur J Neurosci, 25*(7), 2201-2213. doi: 10.1111/j.1460-9568.2007.05473.x
Erdtmann-Vourliotis, M., Mayer, P., Riechert, U., Grecksch, G., & Hollt, V. (1998). Identification of brain regions that are markedly activated by morphine in tolerant but not in naive rats. *Brain Res Mol Brain Res, 61*(1-2), 51-61.
Fan, L. W., Tanaka, S., Park, Y., Sasaki, K., Ma, T., Tien, L. T., . . . Ho, I. K. (2002). Butorphanol dependence and withdrawal decrease hippocampal kappa 2-opioid receptor binding. *Brain Res, 958*(2), 277-290.
Fan, L. W., Tanaka, S., Tien, L. T., Ma, T., Rockhold, R. W., & Ho, I. K. (2002). Withdrawal from dependence upon butorphanol uniquely increases kappa(1)-opioid receptor binding in the rat brain. *Brain Res Bull, 58*(2), 149-160.
Fellin, T., & Carmignoto, G. (2004). Neurone-to-astrocyte signalling in the brain represents a distinct multifunctional unit. *J Physiol, 559*(Pt 1), 3-15. doi: 10.1113/jphysiol.2004.063214
Festa, E. D., Cecala, C., Quinones-Jenab, V., & Jenab, S. (2002). Cocaine modulates mu-opioid receptor mRNA but not c-fos mRNA levels in primary cortical astrocytes. *Brain Res Bull, 58*(3), 285-288.
Fujita, Y., Kunitachi, S., Iyo, M., & Hashimoto, K. (2012). The antibiotic minocycline prevents methamphetamine-induced rewarding effects in mice. *Pharmacol Biochem Behav, 101*(2), 303-306. doi: 10.1016/j.pbb.2012.01.005
Fumagalli, F., Di Pasquale, L., Caffino, L., Racagni, G., & Riva, M. A. (2008). Stress and cocaine interact to modulate basic fibroblast growth factor (FGF-2) expression in rat brain. *Psychopharmacology (Berl), 196*(3), 357-364. doi: 10.1007/s00213-007-0966-x
Gardell, L. R., King, T., Ossipov, M. H., Rice, K. C., Lai, J., Vanderah, T. W., & Porreca, F. (2006). Opioid receptor-mediated hyperalgesia and antinociceptive tolerance induced by sustained opiate delivery. *Neurosci Lett, 396*(1), 44-49. doi: 10.1016/j.neulet.2005.11.009

Garrido, E., Perez-Garcia, C., Alguacil, L. F., & Diez-Fernandez, C. (2005). The alpha2-adrenoceptor antagonist yohimbine reduces glial fibrillary acidic protein upregulation induced by chronic morphine administration. *Neurosci Lett, 383*(1-2), 141-144. doi: 10.1016/j.neulet.2005.04.002

Glass, M. J., & Pickel, V. M. (2002). Alpha(2A)-adrenergic receptors are present in mu-opioid receptor containing neurons in rat medial nucleus tractus solitarius. *Synapse, 43*(3), 208-218. doi: 10.1002/syn.10036

Han, J. S., & Xie, C. W. (1984). Dynorphin: potent analgesic effect in spinal cord of the rat. *Sci Sin B, 27*(2), 169-177.

Hassel, B., Paulsen, R. E., Johnsen, A., & Fonnum, F. (1992). Selective inhibition of glial cell metabolism in vivo by fluorocitrate. *Brain Res, 576*(1), 120-124.

Hauser, K. F., Stiene-Martin, A., Mattson, M. P., Elde, R. P., Ryan, S. E., & Godleske, C. C. (1996). mu-Opioid receptor-induced Ca2+ mobilization and astroglial development: morphine inhibits DNA synthesis and stimulates cellular hypertrophy through a Ca(2+)-dependent mechanism. *Brain Res, 720*(1-2), 191-203. doi: 10.1016/0006-8993(96)00103-5

Haydon, P. G., Blendy, J., Moss, S. J., & Rob Jackson, F. (2009). Astrocytic control of synaptic transmission and plasticity: a target for drugs of abuse? *Neuropharmacology, 56 Suppl 1*, 83-90. doi: 10.1016/j.neuropharm.2008.06.050

Hemby, S. E., Co, C., Koves, T. R., Smith, J. E., & Dworkin, S. I. (1997). Differences in extracellular dopamine concentrations in the nucleus accumbens during response-dependent and response-independent cocaine administration in the rat. *Psychopharmacology (Berl), 133*(1), 7-16.

Hemby, S. E., Martin, T. J., Co, C., Dworkin, S. I., & Smith, J. E. (1995). The effects of intravenous heroin administration on extracellular nucleus accumbens dopamine concentrations as determined by in vivo microdialysis. *J Pharmacol Exp Ther, 273*(2), 591-598.

Hertz, L., & Zielke, H. R. (2004). Astrocytic control of glutamatergic activity: astrocytes as stars of the show. *Trends Neurosci, 27*(12), 735-743. doi: 10.1016/j.tins.2004.10.008

Hill, S. J., Barbarese, E., & McIntosh, T. K. (1996). Regional heterogeneity in the response of astrocytes following traumatic brain injury in the adult rat. *J Neuropathol Exp Neurol, 55*(12), 1221-1229.

Hong, J., Cho, I. H., Kwak, K. I., Suh, E. C., Seo, J., Min, H. J., . . . Lee, S. J. (2010). Microglial Toll-like receptor 2 contributes to kainic acid-induced glial activation and hippocampal neuronal cell death. *J Biol Chem, 285*(50), 39447-39457. doi: 10.1074/jbc.M110.132522

Horvath, R. J., & DeLeo, J. A. (2009). Morphine enhances microglial migration through modulation of P2X4 receptor signaling. *J Neurosci, 29*(4), 998-1005. doi: 10.1523/jneurosci.4595-08.2009

Horvath, R. J., Landry, R. P., Romero-Sandoval, E. A., & DeLeo, J. A. (2010). Morphine tolerance attenuates the resolution of postoperative pain and enhances spinal microglial p38 and extracellular receptor kinase phosphorylation. *Neuroscience, 169*(2), 843-854. doi: 10.1016/j.neuroscience.2010.05.030

Hsia, J. A., Moss, J., Hewlett, E. L., & Vaughan, M. (1984). ADP-ribosylation of adenylate cyclase by pertussis toxin. Effects on inhibitory agonist binding. *J Biol Chem, 259*(2), 1086-1090.

Hu, S., Chao, C. C., Hegg, C. C., Thayer, S., & Peterson, P. K. (2000). Morphine inhibits human microglial cell production of, and migration towards, RANTES. *J Psychopharmacol, 14*(3), 238-243.

Hutchinson, M. R., Bland, S. T., Johnson, K. W., Rice, K. C., Maier, S. F., & Watkins, L. R. (2007). Opioid-induced glial activation: mechanisms of activation and implications for opioid analgesia, dependence, and reward. *ScientificWorldJournal, 7*, 98-111. doi: 10.1100/tsw.2007.230

Hutchinson, M. R., Lewis, S. S., Coats, B. D., Skyba, D. A., Crysdale, N. Y., Berkelhammer, D. L., . . . Johnson, K. W. (2009). Reduction of opioid withdrawal and potentiation of acute opioid analgesia by systemic AV411 (ibudilast). *Brain Behav Immun, 23*(2), 240-250. doi:

10.1016/j.bbi.2008.09.012
Hutchinson, M. R., Northcutt, A. L., Chao, L. W., Kearney, J. J., Zhang, Y., Berkelhammer, D. L., . . . Watkins, L. R. (2008). Minocycline suppresses morphine-induced respiratory depression, suppresses morphine-induced reward, and enhances systemic morphine-induced analgesia. *Brain Behav Immun, 22*(8), 1248-1256. doi: 10.1016/j.bbi.2008.07.008
Hutchinson, M. R., Shavit, Y., Grace, P. M., Rice, K. C., Maier, S. F., & Watkins, L. R. (2011). Exploring the neuroimmunopharmacology of opioids: an integrative review of mechanisms of central immune signaling and their implications for opioid analgesia. *Pharmacol Rev, 63*(3), 772-810. doi: 10.1124/pr.110.004135
Hutchinson, M. R., Zhang, Y., Brown, K., Coats, B. D., Shridhar, M., Sholar, P. W., . . . Watkins, L. R. (2008). Non-stereoselective reversal of neuropathic pain by naloxone and naltrexone: involvement of toll-like receptor 4 (TLR4). *Eur J Neurosci, 28*(1), 20-29. doi: 10.1111/j.1460-9568.2008.06321.x
Hutchinson, M. R., Zhang, Y., Shridhar, M., Evans, J. H., Buchanan, M. M., Zhao, T. X., . . . Watkins, L. R. (2010). Evidence that opioids may have toll-like receptor 4 and MD-2 effects. *Brain Behav Immun, 24*(1), 83-95. doi: 10.1016/j.bbi.2009.08.004
Hyman, S. E., Malenka, R. C., & Nestler, E. J. (2006). Neural mechanisms of addiction: the role of reward-related learning and memory. *Annu Rev Neurosci, 29*, 565-598. doi: 10.1146/annurev.neuro.29.051605.113009
Kaewsuk, S., Hutamekalin, P., Ketterman, A. J., Khotchabhakdi, N., Govitrapong, P., & Casalotti, S. O. (2001). Morphine induces short-lived changes in G-protein gene expression in rat prefrontal cortex. *Eur J Pharmacol, 411*(1-2), 11-16.
Kalivas, P. W. (2004). Glutamate systems in cocaine addiction. *Curr Opin Pharmacol, 4*(1), 23-29. doi: 10.1016/j.coph.2003.11.002
Kalivas, P. W., & O'Brien, C. (2008). Drug addiction as a pathology of staged neuroplasticity. *Neuropsychopharmacology, 33*(1), 166-180. doi: 10.1038/sj.npp.1301564
Kauer, J. A., & Malenka, R. C. (2007). Synaptic plasticity and addiction. *Nat Rev Neurosci, 8*(11), 844-858. doi: 10.1038/nrn2234
Kegeles, L. S., Zea-Ponce, Y., Abi-Dargham, A., Rodenhiser, J., Wang, T., Weiss, R., . . . Laruelle, M. (1999). Stability of [123I]IBZM SPECT measurement of amphetamine-induced striatal dopamine release in humans. *Synapse, 31*(4), 302-308. doi: 10.1002/(sici)1098-2396(19990315)31:4<302::aid-syn9>3.0.co;2-a
Knapp, P. E., & Hauser, K. F. (1996). mu-Opioid receptor activation enhances DNA synthesis in immature oligodendrocytes. *Brain Res, 743*(1-2), 341-345.
Knapp, P. E., Maderspach, K., & Hauser, K. F. (1998). Endogenous opioid system in developing normal and jimpy oligodendrocytes: mu and kappa opioid receptors mediate differential mitogenic and growth responses. *Glia, 22*(2), 189-201.
Koob, G. F., & Le Moal, M. (2008). Addiction and the brain antireward system. *Annu Rev Psychol, 59*, 29-53. doi: 10.1146/annurev.psych.59.103006.093548
Koob, G. F., & Volkow, N. D. (2010). Neurocircuitry of addiction. *Neuropsychopharmacology, 35*(1), 217-238. doi: 10.1038/npp.2009.110
Kuczenski, R., Segal, D. S., Cho, A. K., & Melega, W. (1995). Hippocampus norepinephrine, caudate dopamine and serotonin, and behavioral responses to the stereoisomers of amphetamine and methamphetamine. *J Neurosci, 15*(2), 1308-1317.
Laird, M. H., Rhee, S. H., Perkins, D. J., Medvedev, A. E., Piao, W., Fenton, M. J., & Vogel, S. N. (2009). TLR4/MyD88/PI3K interactions regulate TLR4 signaling. *J Leukoc Biol, 85*(6), 966-977. doi: 10.1189/jlb.1208763
Ledeboer, A., Hutchinson, M. R., Watkins, L. R., & Johnson, K. W. (2007). Ibudilast (AV-411). A new class therapeutic candidate for neuropathic pain and opioid withdrawal syndromes. *Expert Opin Investig Drugs, 16*(7), 935-950. doi: 10.1517/13543784.16.7.935

Ledeboer, A., Sloane, E. M., Milligan, E. D., Frank, M. G., Mahony, J. H., Maier, S. F., & Watkins, L. R. (2005). Minocycline attenuates mechanical allodynia and proinflammatory cytokine expression in rat models of pain facilitation. *Pain, 115*(1-2), 71-83. doi: 10.1016/j.pain.2005.02.009

Ledeboer, A., Wierinckx, A., Bol, J. G., Floris, S., Renardel de Lavalette, C., De Vries, H. E., . . . van dam, A. M. (2003). Regional and temporal expression patterns of interleukin-10, interleukin-10 receptor and adhesion molecules in the rat spinal cord during chronic relapsing EAE. *J Neuroimmunol, 136*(1-2), 94-103.

Lipovsky, M. M., Gekker, G., Hu, S., Hoepelman, A. I., & Peterson, P. K. (1998). Morphine enhances complement receptor-mediated phagocytosis of Cryptococcus neoformans by human microglia. *Clin Immunol Immunopathol, 87*(2), 163-167.

Liu, C. H., Yang, J., Ren, J. Q., Liu, C. M., You, Z., & Liu, P. K. (2013). MRI reveals differential effects of amphetamine exposure on neuroglia in vivo. *Faseb j, 27*(2), 712-724. doi: 10.1096/fj.12-220061

Maderspach, K., Takacs, J., Niewiadomska, G., & Csillag, A. (1995). Postsynaptic and extrasynaptic localization of kappa-opioid receptor in selected brain areas of young rat and chick using an anti-receptor monoclonal antibody. *J Neurocytol, 24*(6), 478-486.

Mallard, C., Wang, X., & Hagberg, H. (2009). The role of Toll-like receptors in perinatal brain injury. *Clin Perinatol, 36*(4), 763-772, v-vi. doi: 10.1016/j.clp.2009.07.009

Mao, J. (2006). Opioid-induced abnormal pain sensitivity. *Curr Pain Headache Rep, 10*(1), 67-70.

Marie-Claire, C., Courtin, C., Roques, B. P., & Noble, F. (2004). Cytoskeletal genes regulation by chronic morphine treatment in rat striatum. *Neuropsychopharmacology, 29*(12), 2208-2215. doi: 10.1038/sj.npp.1300513

Martinez, D., Broft, A., Foltin, R. W., Slifstein, M., Hwang, D. R., Huang, Y., . . . Laruelle, M. (2004). Cocaine dependence and d2 receptor availability in the functional subdivisions of the striatum: relationship with cocaine-seeking behavior. *Neuropsychopharmacology, 29*(6), 1190-1202. doi: 10.1038/sj.npp.1300420

Martinez, D., Gil, R., Slifstein, M., Hwang, D. R., Huang, Y., Perez, A., . . . Abi-Dargham, A. (2005). Alcohol dependence is associated with blunted dopamine transmission in the ventral striatum. *Biol Psychiatry, 58*(10), 779-786. doi: 10.1016/j.biopsych.2005.04.044

McClung, C. A., Ulery, P. G., Perrotti, L. I., Zachariou, V., Berton, O., & Nestler, E. J. (2004). DeltaFosB: a molecular switch for long-term adaptation in the brain. *Brain Res Mol Brain Res, 132*(2), 146-154. doi: 10.1016/j.molbrainres.2004.05.014

McFarland, K., Lapish, C. C., & Kalivas, P. W. (2003). Prefrontal glutamate release into the core of the nucleus accumbens mediates cocaine-induced reinstatement of drug-seeking behavior. *J Neurosci, 23*(8), 3531-3537.

Meller, S. T., Dykstra, C., Grzybycki, D., Murphy, S., & Gebhart, G. F. (1994). The possible role of glia in nociceptive processing and hyperalgesia in the spinal cord of the rat. *Neuropharmacology, 33*(11), 1471-1478.

Merrill, J. E., & Benveniste, E. N. (1996). Cytokines in inflammatory brain lesions: helpful and harmful. *Trends Neurosci, 19*(8), 331-338.

Miguel-Hidalgo, J. J. (2009). The Role of Glial Cells in Drug Abuse. *Curr Drug Abuse Rev, 2*(1), 76-82.

Milligan, E. D., Mehmert, K. K., Hinde, J. L., Harvey, L. O., Martin, D., Tracey, K. J., . . . Watkins, L. R. (2000). Thermal hyperalgesia and mechanical allodynia produced by intrathecal administration of the human immunodeficiency virus-1 (HIV-1) envelope glycoprotein, gp120. *Brain Res, 861*(1), 105-116.

Milligan, E. D., Twining, C., Chacur, M., Biedenkapp, J., O'Connor, K., Poole, S., . . . Watkins, L. R. (2003). Spinal glia and proinflammatory cytokines mediate mirror-image neuropathic pain in rats. *J Neurosci, 23*(3), 1026-1040.

Milton, A. L., & Everitt, B. J. (2010). The psychological and neurochemical mechanisms of drug memory reconsolidation: implications for the treatment of addiction. *Eur J Neurosci, 31*(12), 2308-2319. doi: 10.1111/j.1460-9568.2010.07249.x

Minneman, K. P., & Iversen, I. L. (1976). Enkephalin and opiate narcotics increase cyclic GMP accumulation in slices of rat neostriatum. *Nature, 262*(5566), 313-314.

Narita, M., Aoki, K., Takagi, M., Yajima, Y., & Suzuki, T. (2003). Implication of brain-derived neurotrophic factor in the release of dopamine and dopamine-related behaviors induced by methamphetamine. *Neuroscience, 119*(3), 767-775.

Narita, M., Miyatake, M., Narita, M., Shibasaki, M., Shindo, K., Nakamura, A., . . . Suzuki, T. (2006). Direct evidence of astrocytic modulation in the development of rewarding effects induced by drugs of abuse. *Neuropsychopharmacology, 31*(11), 2476-2488. doi: 10.1038/sj.npp.1301007

Narita, M., Miyatake, M., Shibasaki, M., Tsuda, M., Koizumi, S., Narita, M., . . . Suzuki, T. (2005). Long-lasting change in brain dynamics induced by methamphetamine: enhancement of protein kinase C-dependent astrocytic response and behavioral sensitization. *J Neurochem, 93*(6), 1383-1392. doi: 10.1111/j.1471-4159.2005.03097.x

Nelson, C. L., Milovanovic, M., Wetter, J. B., Ford, K. A., & Wolf, M. E. (2009). Behavioral sensitization to amphetamine is not accompanied by changes in glutamate receptor surface expression in the rat nucleus accumbens. *J Neurochem, 109*(1), 35-51. doi: 10.1111/j.1471-4159.2009.05911.x

Nestler, E. J., & Landsman, D. (2001). Learning about addiction from the genome. *Nature, 409*(6822), 834-835. doi: 10.1038/35057015

Noman, A. S., Koide, N., Hassan, F., I, I. E.-K., Dagvadorj, J., Tumurkhuu, G., . . . Yokochi, T. (2009). Thalidomide inhibits lipopolysaccharide-induced tumor necrosis factor-alpha production via down-regulation of MyD88 expression. *Innate Immun, 15*(1), 33-41. doi: 10.1177/1753425908099317

Obata, K., Katsura, H., Miyoshi, K., Kondo, T., Yamanaka, H., Kobayashi, K., . . . Noguchi, K. (2008). Toll-like receptor 3 contributes to spinal glial activation and tactile allodynia after nerve injury. *J Neurochem, 105*(6), 2249-2259. doi: 10.1111/j.1471-4159.2008.05353.x

Olson, V. G., Zabetian, C. P., Bolanos, C. A., Edwards, S., Barrot, M., Eisch, A. J., . . . Nestler, E. J. (2005). Regulation of drug reward by cAMP response element-binding protein: evidence for two functionally distinct subregions of the ventral tegmental area. *J Neurosci, 25*(23), 5553-5562. doi: 10.1523/jneurosci.0345-05.2005

Parpura, V., & Verkhratsky, A. (2012). Astrocytes revisited: concise historic outlook on glutamate homeostasis and signaling. *Croat Med J, 53*(6), 518-528.

Peterson, P. K., Gekker, G., Hu, S., Sheng, W. S., Molitor, T. W., & Chao, C. C. (1995). Morphine stimulates phagocytosis of Mycobacterium tuberculosis by human microglial cells: involvement of a G protein-coupled opiate receptor. *Adv Neuroimmunol, 5*(3), 299-309.

Philibin, S. D., Hernandez, A., Self, D. W., & Bibb, J. A. (2011). Striatal signal transduction and drug addiction. *Front Neuroanat, 5*, 60. doi: 10.3389/fnana.2011.00060

Pierce, R. C., & Bari, A. A. (2001). The role of neurotrophic factors in psychostimulant-induced behavioral and neuronal plasticity. *Rev Neurosci, 12*(2), 95-110.

Pierce, R. C., Bell, K., Duffy, P., & Kalivas, P. W. (1996). Repeated cocaine augments excitatory amino acid transmission in the nucleus accumbens only in rats having developed behavioral sensitization. *J Neurosci, 16*(4), 1550-1560.

Przewlocka, B., Machelska, H., & Lason, W. (1994). Kappa opioid receptor agonists inhibit the pilocarpine-induced seizures and toxicity in the mouse. *Eur Neuropsychopharmacol, 4*(4), 527-533.

Pubill, D., Canudas, A. M., Pallas, M., Camins, A., Camarasa, J., & Escubedo, E. (2003). Different glial response to methamphetamine- and methylenedioxymethamphetamine-induced

neurotoxicity. *Naunyn Schmiedebergs Arch Pharmacol, 367*(5), 490-499. doi: 10.1007/s00210-003-0747-y

Raghavendra, V., Tanga, F., & DeLeo, J. A. (2003). Inhibition of microglial activation attenuates the development but not existing hypersensitivity in a rat model of neuropathy. *J Pharmacol Exp Ther, 306*(2), 624-630. doi: 10.1124/jpet.103.052407

Raghavendra, V., Tanga, F. Y., & DeLeo, J. A. (2004). Attenuation of morphine tolerance, withdrawal-induced hyperalgesia, and associated spinal inflammatory immune responses by propentofylline in rats. *Neuropsychopharmacology, 29*(2), 327-334. doi: 10.1038/sj.npp.1300315

Rasmussen, S. G., Carroll, F. I., Maresch, M. J., Jensen, A. D., Tate, C. G., & Gether, U. (2001). Biophysical characterization of the cocaine binding pocket in the serotonin transporter using a fluorescent cocaine analogue as a molecular reporter. *J Biol Chem, 276*(7), 4717-4723. doi: 10.1074/jbc.M008067200

Rezaie, P., & Male, D. (2002). Mesoglia & microglia--a historical review of the concept of mononuclear phagocytes within the central nervous system. *J Hist Neurosci, 11*(4), 325-374. doi: 10.1076/jhin.11.4.325.8531

Ricaurte, G. A., Seiden, L. S., & Schuster, C. R. (1984). Further evidence that amphetamines produce long-lasting dopamine neurochemical deficits by destroying dopamine nerve fibers. *Brain Res, 303*(2), 359-364.

Ritz, M. C., Cone, E. J., & Kuhar, M. J. (1990). Cocaine inhibition of ligand binding at dopamine, norepinephrine and serotonin transporters: a structure-activity study. *Life Sci, 46*(9), 635-645.

Rodriguez, J. J., Mackie, K., & Pickel, V. M. (2001). Ultrastructural localization of the CB1 cannabinoid receptor in mu-opioid receptor patches of the rat Caudate putamen nucleus. *J Neurosci, 21*(3), 823-833.

Rusin, K. I., Giovannucci, D. R., Stuenkel, E. L., & Moises, H. C. (1997). Kappa-opioid receptor activation modulates Ca2+ currents and secretion in isolated neuroendocrine nerve terminals. *J Neurosci, 17*(17), 6565-6574.

Ruzicka, B. B., Fox, C. A., Thompson, R. C., Meng, F., Watson, S. J., & Akil, H. (1995). Primary astroglial cultures derived from several rat brain regions differentially express mu, delta and kappa opioid receptor mRNA. *Brain Res Mol Brain Res, 34*(2), 209-220.

Ruzicka, B. B., Thompson, R. C., Watson, S. J., & Akil, H. (1996). Interleukin-1 beta-mediated regulation of mu-opioid receptor mRNA in primary astrocyte-enriched cultures. *J Neurochem, 66*(1), 425-428.

Saal, D., Dong, Y., Bonci, A., & Malenka, R. C. (2003). Drugs of abuse and stress trigger a common synaptic adaptation in dopamine neurons. *Neuron, 37*(4), 577-582.

Schwarz, J. M., & Bilbo, S. D. (2013). Adolescent morphine exposure affects long-term microglial function and later-life relapse liability in a model of addiction. *J Neurosci, 33*(3), 961-971. doi: 10.1523/jneurosci.2516-12.2013

Schwarz, J. M., & Bilbo, S. D. (2013). Adolescent morphine exposure affects long-term microglial function and later-life relapse liability in a model of addiction. *J Neurosci, 33*(3), 961-971. doi: 10.1523/jneurosci.2516-12.2013

Shanks, R. A., Anderson, J. R., Taylor, J. R., & Lloyd, S. A. (2012). Amphetamine and methamphetamine have a direct and differential effect on BV2 microglia cells. *Bull Exp Biol Med, 154*(2), 228-232.

Shavit, Y., Wolf, G., Goshen, I., Livshits, D., & Yirmiya, R. (2005). Interleukin-1 antagonizes morphine analgesia and underlies morphine tolerance. *Pain, 115*(1-2), 50-59. doi: 10.1016/j.pain.2005.02.003

Sibinga, N. E., & Goldstein, A. (1988). Opioid peptides and opioid receptors in cells of the immune system. *Annu Rev Immunol, 6*, 219-249. doi: 10.1146/annurev.iy.06.040188.001251

Silvia, C. P., Jaber, M., King, G. R., Ellinwood, E. H., & Caron, M. G. (1997). Cocaine and

amphetamine elicit differential effects in rats with a unilateral injection of dopamine transporter antisense oligodeoxynucleotides. *Neuroscience, 76*(3), 737-747.
Smith, K. (2010). Neuroscience: Settling the great glia debate. *Nature, 468*(7321), 160-162. doi: 10.1038/468160a
Snider, S. E., Hendrick, E. S., & Beardsley, P. M. (2013). Glial cell modulators attenuate methamphetamine self-administration in the rat. *Eur J Pharmacol, 701*(1-3), 124-130. doi: 10.1016/j.ejphar.2013.01.016
Snider, S. E., Hendrick, E. S., & Beardsley, P. M. (2013). Glial cell modulators attenuate methamphetamine self-administration in the rat. *Eur J Pharmacol, 701*(1-3), 124-130. doi: 10.1016/j.ejphar.2013.01.016
Song, P., & Zhao, Z. Q. (2001). The involvement of glial cells in the development of morphine tolerance. *Neurosci Res, 39*(3), 281-286.
Sun, X., Zhao, Y., & Wolf, M. E. (2005). Dopamine receptor stimulation modulates AMPA receptor synaptic insertion in prefrontal cortex neurons. *J Neurosci, 25*(32), 7342-7351. doi: 10.1523/jneurosci.4603-04.2005
Sutton, M. A., Schmidt, E. F., Choi, K. H., Schad, C. A., Whisler, K., Simmons, D., . . . Self, D. W. (2003). Extinction-induced upregulation in AMPA receptors reduces cocaine-seeking behaviour. *Nature, 421*(6918), 70-75. doi: 10.1038/nature01249
Sweitzer, S. M., Schubert, P., & DeLeo, J. A. (2001). Propentofylline, a glial modulating agent, exhibits antiallodynic properties in a rat model of neuropathic pain. *J Pharmacol Exp Ther, 297*(3), 1210-1217.
Takayama, N., & Ueda, H. (2005). Morphine-induced chemotaxis and brain-derived neurotrophic factor expression in microglia. *J Neurosci, 25*(2), 430-435. doi: 10.1523/jneurosci.3170-04.2005
Taussig, R., Iniguez-Lluhi, J. A., & Gilman, A. G. (1993). Inhibition of adenylyl cyclase by Gi alpha. *Science, 261*(5118), 218-221.
Tawfik, V. L., LaCroix-Fralish, M. L., Nutile-McMenemy, N., & DeLeo, J. A. (2005). Transcriptional and translational regulation of glial activation by morphine in a rodent model of neuropathic pain. *J Pharmacol Exp Ther, 313*(3), 1239-1247. doi: 10.1124/jpet.104.082420
Thorlin, T., Eriksson, P. S., Persson, P. A., Aberg, N. D., Hansson, E., & Ronnback, L. (1998). Delta-opioid receptors on astroglial cells in primary culture: mobilization of intracellular free calcium via a pertussis sensitive G protein. *Neuropharmacology, 37*(3), 299-311.
Tirumalai, P. S., & Howells, R. D. (1994). Regulation of calbindin-D28K gene expression in response to acute and chronic morphine administration. *Brain Res Mol Brain Res, 23*(1-2), 144-150.
Toda, N., Kishioka, S., Hatano, Y., & Toda, H. (2009). Modulation of opioid actions by nitric oxide signaling. *Anesthesiology, 110*(1), 166-181. doi: 10.1097/ALN.0b013e31819146a9
Todtenkopf, M. S., Parsegian, A., Naydenov, A., Neve, R. L., Konradi, C., & Carlezon, W. A., Jr. (2006). Brain reward regulated by AMPA receptor subunits in nucleus accumbens shell. *J Neurosci, 26*(45), 11665-11669. doi: 10.1523/jneurosci.3070-06.2006
Traynelis, S. F., Wollmuth, L. P., McBain, C. J., Menniti, F. S., Vance, K. M., Ogden, K. K., . . . Dingledine, R. (2010). Glutamate receptor ion channels: structure, regulation, and function. *Pharmacol Rev, 62*(3), 405-496. doi: 10.1124/pr.109.002451
Trescot, A. M., Datta, S., Lee, M., & Hansen, H. (2008). Opioid pharmacology. *Pain Physician, 11*(2 Suppl), S133-153.
Tryoen-Toth, P., Gaveriaux-Ruff, C., Maderspach, K., & Labourdette, G. (1998). Regulation of kappa-opioid receptor mRNA level by cyclic AMP and growth factors in cultured rat glial cells. *Brain Res Mol Brain Res, 55*(1), 141-150.
Tuncel, M., Wang, Z., Arbique, D., Fadel, P. J., Victor, R. G., & Vongpatanasin, W. (2002). Mechanism of the blood pressure--raising effect of cocaine in humans. *Circulation, 105*(9),

1054-1059.
UNODC,World Drug Report 2012 (United Nations World Drug Report 2012 (United Nations publication, Sales No. E.12.XI.1),UNITED NATIONS, New York, 2012, pp. preface-iii,1
Vanderah, T. W., Gardell, L. R., Burgess, S. E., Ibrahim, M., Dogrul, A., Zhong, C. M., . . . Porreca, F. (2000). Dynorphin promotes abnormal pain and spinal opioid antinociceptive tolerance. *J Neurosci, 20*(18), 7074-7079.
Vanderah, T. W., Ossipov, M. H., Lai, J., Malan, T. P., Jr., & Porreca, F. (2001). Mechanisms of opioid-induced pain and antinociceptive tolerance: descending facilitation and spinal dynorphin. *Pain, 92*(1-2), 5-9.
Viviani, B., Bartesaghi, S., Gardoni, F., Vezzani, A., Behrens, M. M., Bartfai, T., . . . Marinovich, M. (2003). Interleukin-1beta enhances NMDA receptor-mediated intracellular calcium increase through activation of the Src family of kinases. *J Neurosci, 23*(25), 8692-8700.
Volkow, N. D., Fowler, J. S., Wang, G. J., Swanson, J. M., & Telang, F. (2007). Dopamine in drug abuse and addiction: results of imaging studies and treatment implications. *Arch Neurol, 64*(11), 1575-1579. doi: 10.1001/archneur.64.11.1575
Volkow, N. D., Wang, G. J., Fischman, M. W., Foltin, R., Fowler, J. S., Franceschi, D., . . . Pappas, N. (2000). Effects of route of administration on cocaine induced dopamine transporter blockade in the human brain. *Life Sci, 67*(12), 1507-1515.
Watkins, L. R., Hutchinson, M. R., Rice, K. C., & Maier, S. F. (2009). The "toll" of opioid-induced glial activation: improving the clinical efficacy of opioids by targeting glia. *Trends Pharmacol Sci, 30*(11), 581-591. doi: 10.1016/j.tips.2009.08.002
Weber, M., Scherf, N., Kahl, T., Braumann, U. D., Scheibe, P., Kuska, J. P., . . . Franke, H. (2013). Quantitative analysis of astrogliosis in drug-dependent humans. *Brain Res, 1500*, 72-87. doi: 10.1016/j.brainres.2012.12.048
Weber, M., Scherf, N., Kahl, T., Braumann, U. D., Scheibe, P., Kuska, J. P., . . . Franke, H. (2013). Quantitative analysis of astrogliosis in drug-dependent humans. *Brain Res, 1500*, 72-87. doi: 10.1016/j.brainres.2012.12.048
Wise, R. A., & Munn, E. (1995). Withdrawal from chronic amphetamine elevates baseline intracranial self-stimulation thresholds. *Psychopharmacology (Berl), 117*(2), 130-136.
Wu, H. E., Sun, H. S., Cheng, C. W., & Tseng, L. F. (2006). p38 mitogen-activated protein kinase inhibitor SB203580 reverses the antianalgesia induced by dextro-morphine or morphine in the mouse spinal cord. *Eur J Pharmacol, 550*(1-3), 91-94. doi: 10.1016/j.ejphar.2006.08.060
Xu, H., & Gintzler, A. R. (1992). Opioid enhancement of evoked [Met5]enkephalin release requires activation of cholinergic receptors: possible involvement of intracellular calcium. *Proc Natl Acad Sci U S A, 89*(5), 1978-1982.
Yamada, M., Uchida, K., Hayashi, T., Mine, Y., & Kawase, T. (2004). Vigorous neuronal differentiation of amplified and grafted basic fibroblast growth factor-responsive neurospheres derived from neuroepithelial stem cells. *Cell Transplant, 13*(4), 421-428.
Yao, W. D., Gainetdinov, R. R., Arbuckle, M. I., Sotnikova, T. D., Cyr, M., Beaulieu, J. M., . . . Caron, M. G. (2004). Identification of PSD-95 as a regulator of dopamine-mediated synaptic and behavioral plasticity. *Neuron, 41*(4), 625-638.
Zamponi, G. W., & Snutch, T. P. (2002). Modulating modulation: crosstalk between regulatory pathways of presynaptic calcium channels. *Mol Interv, 2*(8), 476-478. doi: 10.1124/mi.2.8.476