Review article / Artykuł przeglądowy

Influence of psychoactive substances on the immune system and involvement of the brain through immunologically-mediated mechanisms

Wpływ substancji psychoaktywnych na układ odpornościowy i działanie mózgu za pośrednictwem mechanizmów immunologicznych

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Abstract

Dependence continues to be an unsolvable problem. Now, some people become dependent or abuse psychoactive substances as a recreational activity. Many think they can give up any time but many progress to dependence. Although the brain is an immune-privileged organ recent studies suggest neuroinflammation can alter brain function. The focus of this review article is discussing a different aspect of the immune system in drug dependence. Also, the adverse effect of substance abuse on the immune system and the possible outcome is investigated.

Streszczenie

Uzależnienie pozostaje nadal trudnym do rozwiązania problemem. Niektóre osoby uzależniają się lub nadużywają substancji psychoaktywnych w ramach aktywności rekreacyjnej. Wiele z nich uważa, że może zaprzestać tego działania, ale u wielu rozwija się uzależnienie. Chociaż mózg jest organem uprzywilejowanym pod względem odporności, to ostatnie badania sugerują, że stany zapalne układu nerwowego mogą zmieniać funkcjonowanie mózgu. Celem artykułu jest omówienie różnych aspektów działania układu odpornościowego w uzależnieniu od substancji psychoaktywnych, a także niekorzystnego wpływu nadużywania substancji na układ odpornościowy.

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Słowa kluczowe: centrum nagrody, receptory Toll-podobne, zespół odstawienia, cytokinowy i komórkowy układ odpornościowy, hormonalny układ odpornościowy.

Introduction

Long term drug use is a multi-facet illness that requires a multidisciplinary approach [1, 2]. In this sense, an individual that abuses psychoactive substances encounters various types of issues depending on the phase of disease [3]. The brain is an immune-privileged organ and traditionally it is thought brain functions are independent of the immune system especially in dependence [4]. The immune system cannot easily put aside in dependence because many neurologic diseases are immune-based [5]. In order to investigate this hypothesis, different kinds of studies have been constructed to outline the role of the immune system in dependence. Maybe the first early evidence that supports this theory comes from animal studies. It has been observed that after long term opiate treatment, withdrawal syndrome severity is reduced following the destruction of the immune system by radiation [6]. Later studies confirmed the role of immune system signalling in the dependence process in the reward circuit [7]. Aside from the development of dependence, co-morbid diseases like depression occur in the abusing and abstinence period and these problems make successful addiction treatment more complex [8]. Normally, the blood-brain barrier (BBB) protects the brain from certain elements. BBB has different functions in the brain but the most relevant to dependence is protecting the brain against immune system elements. Upon destruction of BBB immune system will access the brain and destroy the brain for any reason that normally causes immune system activation [9]. So there are two problems. Firstly, it should be identified that psychoactive substances can cause the production and expression of immune system elements such as cytokines. Secondly, identifying how BBB can be destructed and how it allows elements of the immune system to enter the brain's inner environment.

Methods

A literature search was conducted mainly in Google Scholar and all the published papers found were investigated and evaluated. Other important indexing databases like Pub Med, Scopus, and Embase were also searched. The included articles were not limited to the time of publication and all the relevant articles (animal studies and human studies) were assessed. Also, the keywords of addiction, substances abuse (all types), the reward centre, Toll-like receptors, withdrawal syndrome, cytokine and cell-mediated immune system and hormonal immune system were used alternatively. Then, the abstract was reviewed to investigate study relevance. The whole article was studied and articles selected for inclusion based on relevance to the topics of this review article.

Discussion

Psychoactive substances and the cell-mediated immune system

Cell-mediated immunity involves different kinds of cells like macrophages, natural killer cells, mast cells, basophils, eosinophils and neutrophils [10]. These cells are in turn subdivided into different subtypes. However, there is a complex relationship among these cells and identifying the exact function is not easy. Since opioids are used as palliative agents against pain and maybe other conditions, this situation suggests different studies be conducted to improve how some people cope with side-effects [11]. Preoperative infections in psychoactive substance abusers suggest immune system impairment. This reduction in immune system function prolongs the recovery of patients in the intensive care unit (ICU) [12]. Other studies also confirm the defective immune system in the presence of psychoactive substances. Acute morphine administration impairs white blood cell function that manifests itself as the defective resistance to herpes infection [13]. Also, withdrawal from opioids may increase susceptibility

to infections in morphine-dependent mice [14]. Morphine causes spleen and thymus size reduction by increasing corticosterone, which is very important in maintaining cell-mediated immunity [15]. Opioid abuse makes individuals susceptible to opportunistic infections such as fungal infections [16]. Other studies about other substances like cannabinoids revealed the presence of type-2 cannabinoid receptors in T-lymphocytes [17]. Cocaine is another prevalent drug of abuse that also suppresses the immune system [18]. Cocaine self-administration is associated with an increase in spleen weight and plasma corticosterone level [19]. Also, cocaine increases the risk of infection [20, 21], negatively affects immunocompetent cells [22] and causes deterioration in the pre-existing immune-deficient state [23]. Furthermore, in the withdrawal period, there is a stress-induced reduction of the immune system [24]. In a human study, cocaine use was associated with a significant adverse effect on B, T cells and also natural killer cells [25]. Cocaine selectively increases the susceptibility of HIV infection by suppressing microRNA-55 in mononuclear cells [26].

Psychoactive substances and the hormonal-mediated immune system

Cytokines are hormonal substances released from immune cells in response to different causes like stress, infection and operations [27]. Studies in substance abuse-related changes of cytokines profiles suggest there is a change in cytokine levels in the period of the abuse. It should be noted that every immune cell can secrete cytokines, and cytokine production, in general, is not limited to only one cell type. In a study on heroin dependent teenagers, T-helper 1 (Th1) cytokines (interleukin-2 (IL-2), tumour necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-g) and T-helper 2 cytokines (IL-4 and IL-10) were reduced significantly in teenagers compared to the healthy control group [28]. In the other study with opioids and cannabinoids, it was also shown that immunosuppression as the consequence of drug abuse is associated with the altered balance of interleukins especially IL-10 and IL-17 [29]. In this respect, inactivation of NF-kappa B plays a crucial role. Cytokines also have been used as predictive factors for dependence in patients that receive opioid and other psychoactive substances for pain management [30]. A study on this issue has well documented that the pain threshold changes along with cytokine profile changes, which is associated with augmented dependence. In a complementary study, treatment with buprenorphine and methadone preserve immune function and cytokine profile and therefore improves dependence therapy and treatment [31]. Other studies on opium addiction revealed other cytokine profile changes like reduction of IL-4, IFN-g, IL-6, and TNF-β [32], and the study showed opium addiction influences cytokine profile after surgery [33]. Studies about other substances like cocaine also proposed immune imbalance in the hormonal division [34]. There are sex differences and the plasma concentration of IL-1β, IL-6, IL-10, and TNF-α were lower in women addicts [35]. Cytokines can be used as predictive factors in dependent people with a history of maltreatment in childhood. Maltreated people had more IL-6, IL-4, and TNF-α than those without a history of maltreatment [36]. Autonomic dysfunction has been shown to influence cytokine profile and therefore it has been recommended to alleviate impairment of the immune system independence period [37].

Interaction of psychoactive substances with the brain through immunologically-mediated mechanisms

The brain is considered an immune-privileged organ and this may bring about the question how the immune system can influence brain function [38]. There is sparse evidence that supports brain function alternation by the external immune system agents. This adverse effect mainly occurs as the corruption of the monocellular layer known as the blood-brain barrier (BBB) protecting the brain from external stimuli. BBB disruption occurs by lipopolysaccharide (LPS) and cytokines [39, 40]. LPS disrupts BBB and immune cells trafficking occurs [41]. Also, there is evidence that immune dysregulation causes behavioural brain diseases [42, 43]. BBB performs broad functions like maintaining brain homeostasis, substance influx and efflux [44]. The breakdown of BBB may result in neuroinflammation and brain diseases. BBB integrity in the reward circuit region as the area that mainly regulates addictive behaviour is of great importance. Disruption of BBB in this region will result in dependence. During the course of inflammation, proinflammatory cytokines will penetrate the brain substructures and will influence brain

function namely as neurotransmitter metabolism, neuroendocrine function and synaptic plasticity [45]. Disruption of BBB has been well documented as a consequence of psychoactive substance abuse administration. Substance abuse destroys tight junction proteins like claudins, occludins and junction adherent molecules, and also scaffolding proteins and zonula occludance (1, 2, and 3) [46]. Acute administration of 3,4-Methylenedioxymethamphetamine induces BBB disruption that results in brain edema [47]. Studies on other abused substances have been revealed confirmatory results with morphine, psychostimulant and methamphetamine [48, 49]. In post-mortems of the alcoholic brain, integrity of BBB was shown to be disrupted [50]. Disturbed substance transport has also been absorbed in BBB after drugs treatment. For example, after methamphetamine administration, glucose transport was impaired [51] and also iron transport after cocaine administration was disturbed [52]. In one study, it has been proposed methamphetamine impairs BBB function by induction of oxidative stress in endothelial cells [53]. In another, BBB in limbic brain areas that are important in dependence was shown to be impaired by high doses of cocaine [54]. These studies highlighted the disrupted BBB as the consequence of psychoactive substance abuse and also that dependence can be developed in those individuals. Also, these facts shed light on new treatment strategies. According to one study, sport reversed the adverse effect of methamphetamine on BBB [55]. Social defeat has recently been known as a synergistic factor that augments the adverse effect of psychoactive substance abuse on BBB [56]. Pre-existing infections like HIV have disrupted BBB integrity and therefore facilitate the entrance of immune system agents into the brain [57].

Recently a novel receptor known as Toll-like receptor 4 (TLR4) in the reward pathway has been identified in the brain [58]. Activation of TLR4, which belongs to the pattern recognition receptor (PRR) family, leads to the release of NF-κB and the activation of the innate immune system [59]. TLR4 is found in the brain and is expressed in astrocytes and microglia cells [60]. Activation of these receptors has been associated with the occurrence of addictive behaviour [61, 62]. The role of TLR4 in other brain diseases has been well illustrated. Activation of these receptors in some areas is protective and has adverse effects in others. By potentiating the innate immune system by activation of TLR4, the idea of developing a vaccine for dependence emerges [63]. However in some conditions, upon activation there is an overproduction of cytokines, which causes neurodegeneration [64]. Opioid studies revealed two types of results. In some conditions, the opioid has a reinforcing effect and in others it is non-reinforcing. Morphine conventionally used as a pain killer can activate myeloid differentiation protein 2 (MD2) and reduce inflammation thus increasing the efficacy of pain killers [65]. In another study, blockage of TLR4 by levoisomer of naloxone reduces the reinforcing effect of morphine. In other studies, a negative result was obtained [66, 67]. In studies with alcohol also TLR4 stimulation showed some behavioural changes in the animal model [68] and in other studies neuroinflammation and degeneration occurred [69]. In one study that investigates the activation of TLR4 in the prefrontal cortex, there was an increase in the emergence of binge drinking [70, 71]. Psychostimulants can also increase the expression of TLR4 [72] though there have contradictory results in this area [73]. Overall, to date conflicting results have been reported and complementary studies have been suggested to resolve these doubts on the function of TLR4 in the dependence process [74].

■ Conclusions

In summary, psychoactive substances harm both the cell-mediated and hormonal immune system. The adverse effect may increase the condition contributing to dependence development. Also, the brain as an immune-privilege organ can be penetrated by disruption of the blood-brain barrier as a consequence of psychoactive substance abuse or other reasons like viral infections. This condition also makes susceptible individuals develop dependence.

Conflict of interest/Konflikt interesów

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Ethics/Etyka

The work described in this article has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) on medical research involving human subjects, Uniform Requirements for manuscripts submitted to biomedical journals and the ethical principles defined in the Farmington Consensus of 1997.

Treści przedstawione w pracy są zgodne z zasadami Deklaracji Helsińskiej odnoszącymi się do badań z udziałem ludzi, ujednoliconymi wymaganiami dla czasopism biomedycznych oraz z zasadami etycznymi określonymi w Porozumieniu z Farmington w 1997 roku.

References/Piśmiennictwo

1. Kaur R, Ambwani SR, Singh S. Endocannabinoid system: a multi-facet therapeutic target. *Curr Clin Pharmacol* 2016; 11(2): 110-7.
2. Goodman DJ, Milliken CU, Theiler RN, Nordstrom BR, Akerman SC. A multidisciplinary approach to the treatment of co-occurring opioid use disorder and posttraumatic stress disorder in pregnancy: a case report. *J Dual Diagn* 2015; 11(3-4): 248-57.
3. Hernandez-Avila CA, Rounsaville BJ, Kranzler HR. Opioid-, cannabis- and alcohol-dependent women show more rapid progression to substance abuse treatment. *Drug Alcohol Depend* 2004; 74(3): 265-72.
4. Galea I, Bechmann I, Perry VH. What is immune privilege (not)? *Trends Immunol* 2007; 28(1): 12-8.
5. Schwartz M, Deczkowska A. Neurological disease as a failure of brain-immune crosstalk: the multiple faces of neuroinflammation. *Trends Immunol* 2016; 37(10): 668-79.
6. Dafny N, Pellis N. Evidence that opiate addiction is in part an immune response: destruction of the immune system by irradiation-altered opiate withdrawal. *Neuropharmacology* 1986; 25(8): 815-8.
7. Hutchinson MR, Watkins LR. Why is neuroimmunopharmacology crucial for the future of addiction research? *Neuropharmacology* 2014; 76: 218-27.
8. Swendsen JD, Merikangas KR. The comorbidity of depression and substance use disorders. *Clin Psychol Rev* 2000; 20(2): 173-89.
9. Neuwelt EA. Mechanisms of disease: the blood-brain barrier. *Neurosurgery* 2004; 54(1): 131-42.
10. Calder PC. The relationship between the fatty acid composition of immune cells and their function. *Prostaglandins, Leukotrienes and Essential Fatty Acids* 2008; 79(3-5): 101-8.
11. Gavériaux-Ruff C, Matthes HW, Peluso J, Kieffer BL. Abolition of morphine-immunosuppression in mice lacking the μ-opioid receptor gene. *Proc Natl Acad Sci* 1998; 95(11): 6326-30.
12. Spies CD, von Dossow V, Eggers V, Jetschmann G, El-Hilali R, Egert J, et al. Altered cell-mediated immunity and increased postoperative infection rate in long-term alcoholic patients. *Anesthesiology* 2004; 100(5): 1088-100.
13. Jamali A, Bamdad T, Soleimanjahi H, Pakdel FG, Arefian E. Acute morphine administration reduces white blood cells' capability to induce innate resistance against HSV-1 infection in BALB/c mice. *Neuroimmunomodulation* 2007; 14(1): 16-23.
14. Jamali A, Soleimanjahi H, Moin M, Mahdavi M, Hashemi H, Sabahi F, et al. Withdrawal from morphine reduces cell-mediated immunity against herpes simplex virus generated by natural immunization. *Neuroimmunomodulation* 2012; 19(4): 229-34.
15. Kim Y-R, Lee S-Y, Shin B-A, Kim K-M. Panax ginseng blocks morphine-induced thymic apoptosis by lowering plasma corticosterone level. *Gen Pharmacol Vasc S* 1999; 32(6): 647-52.
16. Ayatollahi-Mousavi SA, Asadikaram G, Nakhaee N, Izadi A, Keikha N. The effects of opium addiction on the immune system function in patients with fungal infection. *Addiction & Health* 2016; 8(4): 218.

17. Mackie K. Cannabinoid receptors as therapeutic targets. *Annu Rev Pharmacol Toxicol* 2006; 46: 101-22.
18. Marasco CC, Goodwin CR, Winder DG, Schramm-Sapyta NL, McLean JA, Wikswo JP. Systems-level view of cocaine addiction: the interconnection of the immune and nervous systems. *Exp Biol Med* 2014; 239(11): 1433-42.
19. Kubera M, Filip M, Budziszewska B, Basta-Kaim A, Wydra K, Leskiewicz M, et al. Immunosuppression induced by a conditioned stimulus associated with cocaine self-administration. *J Pharmacol Sci* 2008; 107(4): 361-9.
20. Ersche KD, Döffinger R. Inflammation and infection in human cocaine addiction. *Curr Opin Behav Sci* 2017; 13: 203-9.
21. Kim SG, Jung JB, Dixit D, Rovner Jr R, Zack JA, Baldwin GC, et al. Cocaine exposure enhances permissiveness of quiescent T cells to HIV infection. *J Leukoc Biol* 2013; 94(4): 835-43.
22. Xu W, Flick T, Mitchel J, Knowles C, Ault K. Cocaine effects on immunocompetent cells: an observation of in vitro cocaine exposure. *Int J Immunopharmacol* 1999; 21(7): 463-72.
23. Roth MD, Tashkin DP, Choi R, Jamieson BD, Zack JA, Baldwin GC. Cocaine enhances human immunodeficiency virus replication in a model of severe combined immunodeficient mice implanted with human peripheral blood leukocytes. *J Infec Dis* 2002; 185(5): 701-5.
24. Avila AH, Morgan CA, Bayer BM. Stress-induced suppression of the immune system after withdrawal from chronic cocaine. *J Pharmacol Exp Ther* 2003; 305(1): 290-7.
25. Zaparte A, Schuch JB, Viola TW, Baptista TA, Beidacki AS, do Prado CH, et al. Cocaine use disorder is associated with changes in Th1/Th2/Th17 cytokines and lymphocytes subsets. *Front Immunol* 2019; 10: 2435.
26. Napuri J, Pilakka-Kanthikeel S, Raymond A, Agudelo M, Yndart-Arias A, Saxena SK, et al. Cocaine enhances HIV-1 infectivity in monocyte derived dendritic cells by suppressing microRNA-155. *PloS One* 2013; 8(12): e83682.
27. Dinarello CA. Historical insights into cytokines. *Eur J Immunol* 2007; 37(S1): S34-S45.
28. Kuang Y, Zhu Y, Kuang Y, Sun Y, Hua C, He W. Changes of the immune cells, cytokines and growth hormone in teenager drug addicts. *Chinese Journal of Cellular and Molecular Immunology* 2007; 23(9): 821-3.
29. Abo-Elnazar S, Moaaz M, Ghoneim H, Molokhia T, El-Korany W. Th17/Treg imbalance in opioids and cannabinoids addiction: Relationship to NF-κB activation in CD4+ T cells. *Egypt J Immunol* 2014; 21(2): 33-47.
30. Nevidimova T, Batukhtina E, Vetlugina T, Savochkina D, Nikitina V, Lobacheva O, et al. Association of cytokine production with hormone level and sensory responses during the formation of psychoactive drug addiction in men. *Bull Exp Biol Med* 2015; 159(6): 768.
31. Sacerdote P, Franchi S, Gerra G, Leccese V, Panerai AE, Somaini L. Buprenorphine and methadone maintenance treatment of heroin addicts preserves immune function. *Brain Behav Immun* 2008; 22(4): 606-13.
32. Nabati S, Asadikaram G, Arababadi MK, Shahabinejad G, Rezaeian M, Mahmoodi M, et al. The plasma levels of the cytokines in opium-addicts and the effects of opium on the cytokines secretion by their lymphocytes. *Immunol Lett* 2013; 152(1): 42-6.
33. Lashkarizadeh MR, Garshasbi M, Shabani M, Dabiri S, Hadavi H, Manafi-Anari H. Impact of opium addiction on levels of pro- and anti-inflammatory cytokines after surgery. *Addiction & Health* 2016; 8(1): 9.
34. Fiala M, Gan X-H, Zhang L, House S, Newton T, Graves M, et al. *Cocaine enhances monocyte migration across the blood-brain barrier.* Drugs of Abuse, Immunomodulation, and Aids: Springer; 1998, p. 199-205.
35. Pedraz M, Araos P, García-Marchena N, Serrano A, Romero-Sanchiz P, Suárez J, et al. Sex differences in psychiatric comorbidity and plasma biomarkers for cocaine addiction in abstinent cocaine-addicted subjects in outpatient settings. *Front Psychiatry* 2015; 6: 17.

36. Levandowski ML, Viola TW, Prado CH, Wieck A, Bauer ME, Brietzke E, et al. Distinct behavioral and immunoendocrine parameters during crack cocaine abstinence in women reporting childhood abuse and neglect. *Drug Alcohol Depend* 2016; 167: 140-8.
37. Irwin MR, Olmos L, Wang M, Valladares EM, Motivala SJ, Fong T, et al. Cocaine dependence and acute cocaine induce decreases of monocyte proinflammatory cytokine expression across the diurnal period: autonomic mechanisms. *J Pharmacol Exp Ther* 2007; 320(2): 507-15.
38. Pachter JS, de Vries HE, Fabry Z. The blood-brain barrier and its role in immune privilege in the central nervous system. *J Neuropathol Exp Neurol* 2003; 62(6): 593-604.
39. Liebner S, Czupalla CJ, Wolburg H. Current concepts of blood-brain barrier development. *Int J Dev Biol* 2011; 55(4-5): 467-76.
40. Verma S, Nakaoke R, Dohgu S, Banks WA. Release of cytokines by brain endothelial cells: a polarized response to lipopolysaccharide. *Brain Behav Immun* 2006; 20(5): 449-55.
41. Banks WA, Erickson MA. The blood-brain barrier and immune function and dysfunction. *Neurobiol Dis* 2010; 37(1): 26-32.
42. Neumann H, Wekerle H. Neuronal control of the immune response in the central nervous system: linking brain immunity to neurodegeneration. *J Neuropathol Exp Neurol* 1998; 57(1): 1.
43. Crews FT. Immune function genes, genetics, and the neurobiology of addiction. *Alcohol Res: Curr Rev* 2012; 34(3): 355.
44. Obermeier B, Daneman R, Ransohoff RM. Development, maintenance and disruption of the blood-brain barrier. *Nat Med* 2013; 19(12): 1584.
45. Capuron L, Miller AH. Immune system to brain signaling: neuropsychopharmacological implications. *Pharmacol Ther* 2011; 130(2): 226-38.
46. Pimentel E, Sivalingam K, Doke M, Samikkannu T. Effects of drugs of abuse on the blood-brain barrier: a brief overview. *Front Neurosci* 2020; 14: 513.
47. Sharma HS, Ali SF. Acute Administration of 3, 4-Methylenedioxymethamphetamine Induces Profound Hyperthermia, Blood–Brain Barrier Disruption, Brain Edema Formation, and Cell Injury: An Experimental Study in Rats and Mice Using Biochemical and Morphologic Approaches. *Ann N Y Acad Sci* 2008; 1139(1): 242-58.
48. Sharma HS, Ali SF. Alterations in blood–brain barrier function by morphine and methamphetamine. *Ann N Y Acad Sci* 2006; 1074(1): 198-224.
49. Kousik SM, Napier TC, Carvey PM. The effects of psychostimulant drugs on blood brain barrier function and neuroinflammation. *Front Pharmacol* 2012; 3: 121.
50. Rubio-Araiz A, Porcu F, Pérez-Hernández M, García-Gutiérrez MS, Aracil-Fernández MA, Gutierrez-López MD, et al. Disruption of blood–brain barrier integrity in postmortem alcoholic brain: preclinical evidence of TLR4 involvement from a binge-like drinking model. *Addict Biol* 2017; 22(4): 1103-16.
51. Muneer PA, Alikunju S, Szlachetka AM, Murrin LC, Haorah J. Impairment of brain endothelial glucose transporter by methamphetamine causes blood-brain barrier dysfunction. *Mol Neurodegener* 2011; 6(1): 1-13.
52. Ersche KD, Acosta-Cabronero J, Jones P, Ziauddeen H, Van Swelm R, Laarakkers C, et al. Disrupted iron regulation in the brain and periphery in cocaine addiction. *Transl Psychiatry* 2017; 7(2): e1040.
53. Ramirez SH, Potula R, Fan S, Eidem T, Papugani A, Reichenbach N, et al. Methamphetamine disrupts blood–brain barrier function by induction of oxidative stress in brain endothelial cells. *J Cereb Blood Flow Metab* 2009; 29(12): 1933-45.
54. Bowyer JF, Ali S. High doses of methamphetamine that cause disruption of the blood-brain barrier in limbic regions produce extensive neuronal degeneration in mouse hippocampus. *Synapse* 2006; 60(7): 521-32.
55. Toborek M, Seelbach MJ, Rashid CS, András IE, Chen L, Park M, et al. Voluntary exercise protects against methamphetamine-induced oxidative stress in brain microvasculature and disruption of the blood–brain barrier. *Mol Neurodegener* 2013; 8(1): 1-11.
56. Rodríguez-Arias M, Montagud-Romero S, Rubio-Araiz A, Aguilar MA, Martín-García E, Cabrera R, et al. Effects of repeated social defeat on adolescent mice on cocaine-induced

CPP and self-administration in adulthood: integrity of the blood–brain barrier. *Addict Biol* 2017; 22(1): 129-41.
57. Atluri VSR, Hidalgo M, Samikkannu T, Kurapati KRV, Jayant RD, Sagar V, et al. Effect of human immunodeficiency virus on blood-brain barrier integrity and function: an update. *Front Cell Neurosci* 2015; 9: 212.
58. Crews FT, Walter TJ, Coleman LG, Vetreno RP. Toll-like receptor signaling and stages of addiction. *Psychopharmacology* 2017; 234(9-10): 1483-98.
59. Vaure C, Liu Y. A comparative review of toll-like receptor 4 expression and functionality in different animal species. *Front Immun* 2014; 5: 316.
60. Kashima DT, Grueter BA. Toll-like receptor 4 deficiency alters nucleus accumbens synaptic physiology and drug reward behavior. *Proc Natl Acad Sci* 2017; 114(33): 8865-70.
61. Northcutt A, Hutchinson M, Wang X, Baratta M, Hiranita T, Cochran T, et al. DAT isn't all that: cocaine reward and reinforcement require Toll-like receptor 4 signaling. *Mol Psychiatry* 2015; 20(12): 1525-37.
62. June HL, Liu J, Warnock KT, Bell KA, Balan I, Bollino D, et al. CRF-amplified neuronal TLR4/MCP-1 signaling regulates alcohol self-administration. *Neuropsychopharmacology* 2015; 40(6): 1549-59.
63. Kosten T, Domingo C, Orson F, Kinsey B. Vaccines against stimulants: cocaine and MA. *Br J Clin Pharmacol* 2014; 77(2): 368-74.
64. Zhang K, Wang H, Xu M, Frank JA, Luo J. Role of MCP-1 and CCR2 in ethanol-induced neuroinflammation and neurodegeneration in the developing brain. *J Neuroinflammation* 2018; 15(1): 1-14.
65. Wang X, Loram LC, Ramos K, de Jesus AJ, Thomas J, Cheng K, et al. Morphine activates neuroinflammation in a manner parallel to endotoxin. *Proc Natl Acad Sci* 2012; 109(16): 6325-30.
66. Skolnick P, Davis H, Arnelle D, Deaver D. Translational potential of naloxone and naltrexone as TLR4 antagonists. *Trends Pharmacol Sci* 2014; 35(9): 431-2.
67. Stevens CW, Aravind S, Das S, Davis R. Pharmacological characterization of LPS and opioid interactions at the toll-like receptor 4. *Br J Pharmacol* 2013; 168(6): 1421-9.
68. Blednov YA, Black M, Benavidez JM, Da Costa A, Mayfield J, Harris RA. Sedative and Motor Incoordination Effects of Ethanol in Mice Lacking CD 14, TLR 2, TLR 4, or MyD88. *Alcohol Clin Exp Res* 2017; 41(3): 531-40.
69. Alfonso-Loeches S, Pascual M, Gómez-Pinedo U, Pascual-Lucas M, Renau-Piqueras J, Guerri C. Toll-like receptor 4 participates in the myelin disruptions associated with chronic alcohol abuse. *Glia* 2012; 60(6): 948-64.
70. Vetreno RP, Crews FT. Adolescent binge drinking increases expression of the danger signal receptor agonist HMGB1 and Toll-like receptors in the adult prefrontal cortex. *Neuroscience* 2012; 226: 475-88.
71. Famitafreshi H, Karimian M, Afshari M. Susceptibility of Drug-seeking and Taking Behaviors Increases through Dysregulation of Copper and Zinc and Impaired Prefrontal Function in Addiction Period in Male Rats. *Int J Biochem Res Rev* 2016; 13(3): 1-8.
72. Periyasamy P, Liao K, Kook YH, Niu F, Callen SE, Guo M-L, et al. Cocaine-mediated downregulation of miR-124 activates microglia by targeting KLF4 and TLR4 signaling. *Mol Neurobiol* 2018; 55(4): 3196-210.
73. Tanda G, Mereu M, Hiranita T, Quarterman JC, Coggiano M, Katz JL. Lack of specific involvement of (+)-naloxone and (+)-naltrexone on the reinforcing and neurochemical effects of cocaine and opioids. *Neuropsychopharmacology* 2016; 41(11): 2772-81.
74. Wu R, Li J-X. Toll-Like Receptor 4 Signaling and Drug Addiction. *Front Pharmacol* 2020; 11. DOI: https://doi.org/10.3389/fphar.2020.603445.