Current Neuropharmacology, 2022, *20,* 2142-2155

REVIEW ARTICLE

A Possible Causal Involvement of Neuroinflammatory, Purinergic P2X7 Receptors in Psychiatric Disorders

Ying Zhang[1,2], Hai-Yan Yin[1], Patrizia Rubini[1,2], Yong Tang[1,2,*] and Peter Illes[1,2,3,*]

[1]*School of Acupuncture and Tuina, Chengdu University of Traditional Chinese Medicine, Chengdu 610075, China;* [2]*International Collaborative Centre on Big Science Plan for Purinergic Signalling, Chengdu University of Traditional Chinese Medicine, Chengdu 610075, China;* [3]*Rudolf Boehm Institute for Pharmacology and Toxicology, University of Leipzig, 04109 Leipzig, Germany*

ARTICLE HISTORY

Received: December 22, 2021
Revised: January 29, 2022
Accepted: February 26, 2022

DOI:
10.2174/1570159X20666220302152400

Abstract: P2X7 receptors (Rs) are prominent members of the P2XR family, which after binding ATP, open non-selective cationic channels, thereby allowing the transmembrane passage of Na^+, Ca^{2+}, and K^+. Long-lasting and repetitive stimulation of the receptor by its agonist leads to the formation of large membrane pores permeable for organic cations of up to 900 Da molecular size. These pores are believed to play a role in apoptosis and inflammation. P2X7Rs are located primarily at peripheral macrophages and microglial cells, the resident macrophages of the CNS. The co-activation of toll-like receptors 4 (TLR4) by lipopolysaccharide, a constituent of the cell membrane of gram-negative bacteria, and the P2X7R by ATP leads to the generation and release of the pro-inflammatory cytokines interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α. Together with the microglial release of chemokines, reactive oxygen and nitrogen species, proteases, and excitotoxic glutamate, these cytokines result in neurodegeneration. P2X7Rs were found not only to amplify various neurodegenerative illnesses, such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and multiple sclerosis, but also to participate in a range of psychiatric diseases, such as major depression, bipolar disorder, schizophrenia, and autism spectrum disorder. Based on the prevention/reversal of neuroinflammation, pharmacological antagonists of P2X7Rs and their genetic deletion in animal experiments counteract these deleterious psychiatric conditions. Hence, brain penetrant P2X7R antagonists are potential therapeutics for psychiatric diseases, although the available evidence still needs to be extended and validated by further clinical data.

Keywords: P2X7 receptor, psychiatric disorders, neuroinflammation, interleukin-1β, clinical data, neurodegeneration.

1. INTRODUCTION

Psychiatric diseases are typically characterized by a set of clinically pleomorphic symptoms with manifestations of emotional, cognitive, visceral, and behavioral limitations, severely restricting the life quality of afflicted patients. With the high rate of the accompanying disability/death and, in most cases, with their chronic occurrence, they cause immense socioeconomic burden [1]. Generally, most mental disorders are considered to be a result of the combination of different factors and individual susceptibility. However, their pathophysiology is thought to potentially share a related mechanism [2, 3]. Over the past decades, accumulating and compelling evidence indicates that immune cells in the central nervous system (CNS), such as microglia, and their interplay with astrocytes and neurons might have a pivotal role in the pathophysiology of mood disorders, thereby emerging as new targets for therapeutics [4-7]. It has been proposed that depression is attributed to a purine-based control of glia-neuron bidirectional communication that is associated with the up-regulation of microglial P2X7 receptors (Rs), astrocytic hypofunction, and decreased ATP release [8]. An increased level of peripheral inflammatory markers in people with major depressive disorder (MDD), and many cases in which patients with inflammatory and autoimmune diseases experience depression, point to a close association between these illnesses [9-11].

In this review, we provide a summary of the involvement of P2X7Rs in the pathophysiology of several primary psychiatric diseases and underline the importance of neuroinflammation in MDD, bipolar disorder, schizophrenia, and autism spectrum disorder (ASD) (Fig. **1**). We also discuss the recent progress in investigating blood brain barrier-permeable P2X7R antagonists, applicable as possible therapeutic strategies for mental illnesses.

*Address correspondence to these authors at the Rudolf Boehm Institute for Pharmacology and Toxicology, University of Leipzig, 04107, Leipzig, Germany; Tel/Fax: (+49)341-9724614, (+49)341-9724609; E-mail: peter.illes@medizin.uni-leipzig.de or at Acupuncture and Tuina School, Chengdu University of Traditional Chinese Medicine, 610075, Chengdu, China; Tel/Fax: (+86) 28-87689918, (+86) 28-87683962;
E-mail: tangyong@cdutcm.edu.cn

1875-6190/22 $65.00+.00

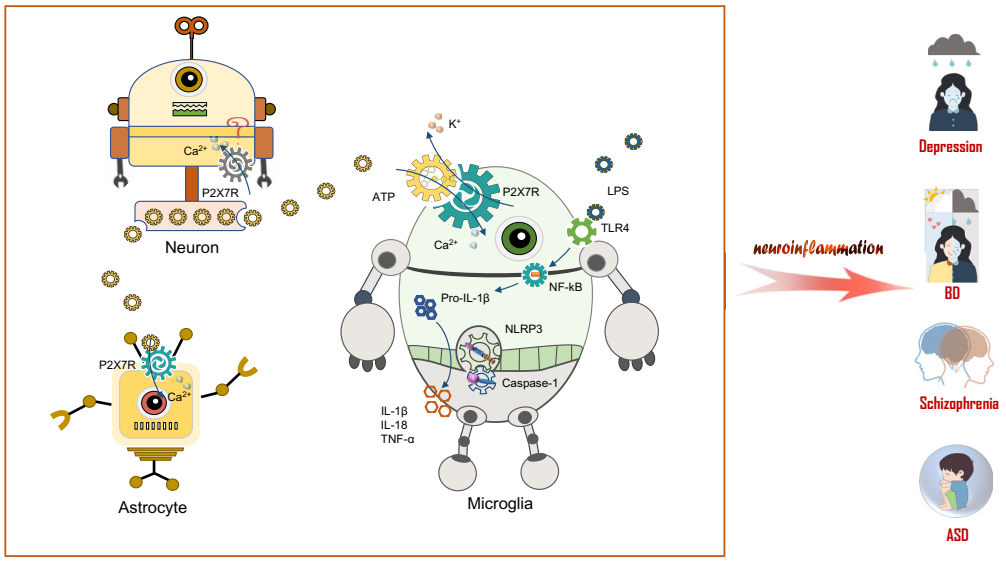

Fig. (1). A simplified scheme of P2X7R functions in microglia, astrocytes, and probably also neurons to induce neuroinflammation as a causative factor of major depression, bipolar disorder, schizophrenia, and autism spectrum disorder (ASD). P2X7Rs are none-selective cationic channels activated by high concentrations of ATP to allow the transmembrane fluxes of Na^+, Ca^{2+}, and K^+. This receptor is, in addition, able to become permeable to large molecules of up to 900 Da on long-lasting or repetitive occupation by ATP. Especially in microglia, P2X7Rs stimulate the P2X7R/NLRP3 inflammasome/caspase-1/interleukin 1β (IL-1β)-pathway after co-activation of toll-like receptor 4 (TLR4) with lipopolysaccharide. The release of the pro-inflammatory cytokines, IL-1β, IL-18, and tumor necrosis factor-α (TNF-α), leads to neuroinflammation. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

2. P2X7RS: CRITICAL PLAYERS IN NEUROINFLAMMATION

P2XRs are ATP-gated membrane channels, built up of three subunits (a linear peptide with a large extracellular loop, two transmembrane regions, and N- and C-terminal ends) permeable to the small cations Na^+, Ca^{2+}, and K^+ [12-14]. P2X7Rs have three distinguishing characteristics in comparison with the other members of this family [15]. (1) They are activated by concentrations of ATP in the high micromolar/millimolar range in contrast to other P2XRs, which are activated already by lower micromolar ATP; (2) Long-lasting or repetitive stimulation by ATP causes the formation of large pores, thereby allowing the transmembrane passage of molecules with the size of up to 900 Da. These pores are believed to play a direct role in apoptosis/pyroptosis and inflammation [16-18]; (3) P2X7Rs have a long C-terminus, which regulates receptor function, including signaling pathways, cellular localization, protein-protein interactions, and post-translational modification [18, 19].

It is noteworthy that originally it was assumed that the cationic channel of P2X7Rs exhibits prominent dilation on long-lasting contact with ATP. This assumption was based on the gradual shift of the equilibrium potential (V_{rev}) as measured with the whole-cell patch-clamp technique when Na^+ in the extracellular medium was substituted with the otherwise impermeable large cation $NMDG^+$ [20]. However, recently time-dependent alterations in the concentration of intracellular ions rather than channel dilation have been found to be the reason for this phenomenon [21]. In support of such a mode of action, the single-channel current amplitudes and permeation characteristics remain constant during the supposed channel dilation [22]. Participation of associated channel-forming proteins also has implications (*e.g.*, pannexin-1; [23]), but convincing evidence now suggests that P2X7Rs by themselves are endowed with the ability to form a large conductance pore [24, 25]. Pannexins are a family of vertebrate proteins identified by their homology to the invertebrate innexins [26]. While innexins are responsible for forming gap junctions in invertebrates, the pannexins have been shown to predominantly exist as large transmembrane channels connecting the intracellular and extracellular space, allowing the passage of ions and small molecules between these two compartments.

P2X7Rs have an abundant expression in microglia, the resident macrophages of the CNS, establishing them as major drivers of neuroinflammation, similar to their inflammatory function in peripheral macrophages [27]. P2X7Rs promote the release of proinflammatory cytokines from microglia after a multistep activation process by other P2Y/P2XRs and the induction of microgliosis following an insult to the CNS [17, 28].

The developmental origin of microglia has been the subject of a long-standing debate, which reached an end a couple of years ago with the recognition that in spite of their similarity to peripheral macrophages, these cells are of different genetic origins. Macrophages are continuously produced in the bone marrow during the post-natal stage, whereas microglia are derived from yolk-sac progenitors migrating into the CNS; this migration starts at embryonic day 8.5 and continues until the blood-brain barrier is formed [29]. Moreover, lineage-specific genes define the microglial transcriptional network and distinguish it from that of tissue-resident macrophages in other organs of the body (Kupffer cells of the liver, marginal zone macrophages of the spleen, alveolar macrophages of the lung) [30].

A massive release of ATP caused by immune cell activation and tissue damage effectively stimulates inflammation.

Activated P2X7Rs further expand the effects of pro-inflammatory agents *via* promoting further ATP release [31]. In addition to the already mentioned triggering of ion fluxes, the outstanding contribution of P2X7Rs is to promote the release of pro-inflammatory cytokines, such as interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α) from microglia and dendritic cells of diverse species [32-34]. P2X7Rs also promote the expression of several chemokines (*e.g.*, chemokine [C-X-C motif] ligand 2; CXCL2) and monocyte chemoattractant protein 1 (MCP-1) in astrocytes and microglia [32, 35, 36]. Moreover, the P2X7R efficiently activates various nuclear factors, such as the nuclear factor of activated T cells 1 (NFATc1) and the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [37].

Previous experiments suggested that extracellular ATP is a powerful driver for the release of mature IL-1β from macrophages; the P2X7R was later identified to mediate this effect [38-40]. A rapid fall in the intracellular K^+ concentration due to the opening of the P2X7R-channel and the resulting outward flux of K^+ [41, 42] is the immediate stimulus for the association and subsequent activation of the nucleotide-binding, leucine-rich repeat, pyrin domain containing 3 (NLRP3) inflammasome [43, 44]. The NLRP3 inflammasome promotes caspase-1 maturation and activation *via* enzymatic degradation of the precursor pro-caspase-1 [45-47]. Protein-protein interaction has been reported to occur between the P2X7R and the inflammasome scaffold proteins NLRP2 and NLRP3. The generation of the NLRP2/P2X7R protein complex necessitates interaction with astrocytic pannexin-1; this has been reported to occur at restricted subplasma membrane sites in microglia [48].

Production of IL-1β represents a multistep process involving synthesis of the immature pro-IL-1β, which is then enzymatically cleaved to mature IL-1β by caspase-1 and is finally released into the extracellular space [49]. The stimulation of Toll-like receptor 4 (TLR4) by lipopolysaccharide (LPS) activates nuclear factor NF-κB, which initiates the production of the inactive precursor molecule pro-IL-1β. Pro-IL-1β is eventually degraded to the mature IL-1β. The conversion of the 31 kDa precursor to the bioactive 17 kDa protein requires immediate cleavage by caspase-1 in order to prevent the rapid decomposition of pro-IL-1β *via* the proteasome [50].

In conclusion, all the above observations indicate that the release of IL-1β occurs by the cooperation of the following two pattern recognition receptors: (1) TLR4 stereotypically detects pathogen-associated molecules (PAMPs), such as lipopolysaccharide, which is a constituent of the cell wall of gram-negative bacteria, and (2) P2X7R, which detects danger-associated molecular patterns (DAMPs), such as ATP released under inflammatory conditions from all types of cells, including immunocytes. TLR4 leads to the accumulation of cytoplasmic pro-IL-1β, and P2X7R promotes inflammasome-mediated caspase-1 activation [51]. At the meeting point of these two pathways, active caspase-1 degrades pro-IL-1β and produces the pro-inflammatory IL-1β.

The P2X7R/NLRP3 axis and inflammatory caspases are also associated with a highly inflammatory form of a lytic programmed cell death termed pyroptosis [27, 52, 53]; the involvement of caspase-1 and caspase-11 was reported for mice and the involvement of caspase-1, caspase-4, and caspase-5 for humans in this cell death reaction [54, 55]. During pyroptosis, increased cellular swelling and plasma membrane permeability occur, and at the same time, IL-1β and IL-18 are secreted, resulting in the promotion of inflammation [56]. Recent evidence identified a pivotal role of P2X7Rs in the sequence of events downhill to non-canonical inflammasome activation since the maturation of caspase-11 caused ATP to release *via* the cleavage of pannexin-1 channels that finally mediated autocrine/paracrine P2X7R activation and therefore pyroptosis [57].

3. P2X7RS ARE POTENTIAL TARGETS FOR THE THERAPY OF PSYCHIATRIC ILLNESSES

Recent evidence on the bidirectional relationship between psychiatric disorders and purine-based neuroinflammation is opening new avenues for investigating the role of stress [58], which is considered to be the main environmental trigger of many psychiatric illnesses [59]. P2X7Rs arguably have a crucial role in stressful situations, which are known to contribute to MDD, bipolar disorder, and probably also schizophrenia and autism spectrum disorder in humans.

Published data suggest that immune cells in the periphery and CNS are critically involved in the pathophysiology of mood disorders [60]. In the CNS, owing to the intact blood-brain barrier and blood-cerebrospinal fluid barrier, peripheral immune cells have only restricted access to the brain; they can, however, penetrate the CNS, causing neuroinflammation due to injury or infection, thus leading to the breakdown of the two mentioned barriers. CNS cells, especially the glial cells (microglia and astrocytes), express membrane receptors and intracellular partners that occupy key positions in the neuroimmune system. A rapidly expanding scientific literature suggests that the activation of P2X7Rs followed by that of NLRP3 induces the release of the proinflammatory cytokines, IL-1β, IL-18, and IL-33 [27, 61, 62]. Especially IL-1β release in the CNS leads eventually to neuroinflammation, which is one major contributor of neuropsychiatric disorders [7, 27, 63, 64], such as major depression [10], bipolar disorder, and schizophrenia [65, 66].

Overwhelming evidence supports a crucial role of the P2X7R-triggered inflammatory pathway in the development of psychiatric disorders. Therefore, the pharmacological blockade of this receptor has been expected to improve such diseases [13, 67]. To date, no specific agonist for the P2X7R has been described; usually, ATP itself or the more potent but also non-selective dibenzoyl-ATP (Bz-ATP) is used for experimental purposes [15]. By contrast, a great number of P2X7R antagonistic substances have been developed as pharmacological tools and possible therapeutics for inflammatory diseases [49]. They are broadly classified into two categories. The first group is represented by suramin or suramin-like compounds, ATP derivatives (trinitrophenyl-ATP, periodate-oxidized ATP), tetrazole derivatives (A-438079, A-839977), and cyanoguanidine derivatives (A-740003, A-804598) [68]. Substances from the first group can be only centrally applied, while the second group is also peripherally applicable due to its considerable blood-brain barrier permeability. This one is represented by a class of synthetic negative allosteric modulators [49], which bind to the

brain P2X7R in a dose-dependent manner with a favorable brain/plasma ratio and suppress IL-1β release [8, 62, 69]. JNJ-54175446 is a high-affinity P2X7R antagonist that displays pharmacological activities at recombinant human, rat, mouse, macaque, and dog P2X7Rs, and blocks P2X7R-dependent IL-1β release in humans. JNJ-54175446 and JNJ-55308942 show dose-dependent brain P2X7R occupancy and low blood plasma binding [69, 70].

In addition to small chemical molecules, nanobodies have also been developed for the functional exclusion of P2X7Rs [71, 72]. They are derived from heavy chain antibodies that naturally occur in camelids and display a propensity to bind functional epitopes not accessible to conventional antibodies. It was reported that an anti-mouse P2X7R nanobody (Alb8) with antagonistic properties improved both allergic contact dermatitis and experimental glomerulonephritis in mice [73, 74]. Poor permeability of these nanobodies due to the blood-brain barrier hinders a peripheral application to treat central disorders.

The experimental evidence discussed above strongly suggests that brain permeable P2X7R antagonists are possible therapeutics for major depression and bipolar disorder [75-77]. In 2019, Janssen launched a randomized, placebo-controlled, double-blind, multicenter clinical trial of blood-brain-barrier permeable P2X7R antagonist JNJ-54175446 with the participation of 142 subjects (https://clinicaltrials.gov/ ct2/ show/NCT04116606; [78]. This trial has been carried out in 5 centers of the U.K. by applying 50 mg/kg JNJ-54175446 or placebo daily for 8 weeks and evaluating the success of the treatment on a clinical depression scale. Patients with major depression have been recruited based on their incomplete response to monoaminergic antidepressant drugs, and elevated CRP levels in the blood, indicating an inflammatory component of their disease. The estimated study completion date is June 30, 2022. In the meantime, it was reported that JNJ-54175446 (50-600 mg) exhibited a dose-dependent plasma exposure without any serious adverse events in study participants [79]. The passive brain penetration of the drug was also confirmed. Another multiple ascending dose trial in a range of 50-450 mg showed that JNJ-54175446 was well tolerated by participants, and at doses higher than 100 mg, the drug attenuated dexamphetamine-induced increase in locomotion as measured by saccadic reaction time, saccadic peak velocity, and finger tapping [80]. Thus, presently the available data are encouraging, but we have to wait for more clinical evidence. It is noteworthy that Pfizer, which reduced most of its neuroscience research in 2017, has also been investigating the area of major depression and P2X7R antagonists through its venture capital arm. It recently funded small neurology-focused biotech companies, including MindImmune, which also has a P2X7R inhibitor in its pipeline [78].

4. MAJOR DEPRESSION

The mood disorder MDD is characterized by extreme sadness, depressed mood, and loss of interest that persists at least for 2 weeks and interferes with the individuals' social functioning [67, 81]. A complex interacting network of relevant brain structures has been identified, which consists of neuronal circuitries causally related to depressive-like behavior [82, 83]. As most relevant structures, the medial prefrontal cortex, hippocampus, anterior cingulate cortex, amygdala, nucleus accumbens, ventral tegmental area, lateral habenula, and raphe nucleus emerge, with the prefrontal cortex and hippocampus being especially important.

Linkage studies suggested that variations in chromosome 12q24.31 containing the candidate gene for the P2X7R (P2RX7) may be associated with MDD [16, 84, 85]. It has been suggested that the nonsynonymous single-nucleotide polymorphism rs2230912 coding for Gln460Arg-P2X7R indicates a predisposition for MDD. However, in the meantime, numerous clinical data failed to confirm this assumption [86, 87], and the Psychiatric Genomic Consortium denied the P2RX7 gene as a genetic risk factor for mood disorders in large-scale genome-wide association studies [88].

Nonetheless, the final verdict in this issue is probably still pending. When various P2RX7 single-nucleotide polymorphisms were investigated by electrophysiology/dye uptake studies either in native cells or HEK293 cells transfected with the respective plasmids, several gain-of-function or loss-of-function allelic mutations were identified [89-91]. Surprisingly the ATP-induced inward current was the same through the wild-type receptor and the Gln460Arg polymorphic receptor transfected into HEK293 cells [90]. However, in accordance with the assumed role of this polymorphism in MDD, co-expression of the wild-type P2X7R with the Gln460Arg-P2X7R inhibited calcium influx and current response to ATP [92]. Similarly, conditional humanized mice co-expressing both P2X7R variants showed alterations in their sleep quality, resembling signs of a prodromal MDD state [93].

As an important regulator of neuroinflammation in the CNS, P2X7Rs are highly expressed in microglia and have attracted increasing therapeutic interest in the field of mood disorders [61, 77, 94]. In addition to microglia, P2X7Rs are also expressed in astrocytes and oligodendrocytes, while their presence in neurons is still a matter of debate [95, 96]. Even though the P2X7R expresses abundantly in central immunocytes, it is usually "silent" under normal physiological conditions unless the concentration of ATP reaches high micromolar/millimolar levels to activate the ion channel towards promoting the release of the proinflammatory cytokines IL-1β and IL-18 [61, 97]. Then, IL-1β induces the secretion of corticotropin-releasing hormone in the hypothalamus and the consecutive production of ACTH/glucocorticoids in the hypophysis and adrenal cortex, respectively, resulting in mood disorders. In fact, acute restraint stress was found to rapidly increase the levels of extracellular ATP, as well as that of the inflammatory cytokine IL-1β, and the active form of the NLRP3 inflammasome in the hippocampus of rodents [98]. Intraperitoneal administration of the P2X7R antagonist A-804598 fully inhibited these effects. Moreover, A-804598 reversed the unexpected chronic mild stress (UCMS)-induced anhedonic and anxiety behaviors, measured in the sucrose preference test and elevated plus maze, respectively; furthermore, deletion of the Nlrp3 gene coding for NLRP3 rendered mice resistant to the development of depressive-like behaviors caused by UCMS.

In support of the inflammatory origin of MDD, there is a high degree of comorbidity of MDD with systemic inflam-

matory diseases, including diabetes, cancer, stroke, chronic pain, migraine, and rheumatoid arthritis [99-103]. On the other hand, psychological stress can increase peripheral inflammation in humans, including elevated levels of IL-1β in the blood of patients with MDD [104]. Hence, from a perspective of drug discovery, the P2X7R is an ideal potential therapeutic target for neuroinflammatory disorders of the CNS, including neuropsychiatric diseases [43, 105] (see also Section 8).

Both pharmacological and genetic inhibition of P2X7Rs prevented the development of depressive-like behavior in animal models, supporting the role of P2X7R participation in depression (Table **1**). P2RX7$^{-/-}$ mice exhibited an antidepressant-like profile in tail suspension test (TST) and forced swimming test (FST); this effect was not accompanied by changes in spontaneous locomotor activity [106]. TST and FST induce learned helplessness in rodents; they stop trying to escape when suspended on their tails or stop swimming when having been put into a beaker filled with water. The duration of immobility in these test systems is a measure of the depressive-like state. In P2X7R KO animals, decreased behavioral despair in FST, reduced immobility in TST, and attenuated amphetamine-induced hyperactivity were detected, indicating an antidepressant and antimania phenotype [107-109]. In partial agreement with these findings, another author observed equivalent levels of immobility in P2X7R knockout and wild-type mice on the first exposure to forced swimming, but much greater immobility in the wild-type animals on second and third exposures, in spite of no effect in the knockouts [110]. The genetic deletion of P2X7Rs also impeded the development of depressive- and anxiety-like behaviors induced by UCMS [111]. In contrast to the acute stress models, UCMS was delivered for a couple of weeks and included once daily, for example, immobilization, food deprivation, light/dark phase reversal, hot environment, and cage shaking. Confirming the sequential involvement of P2X7Rs and IL-β in mood disorders in IL-1 receptor null mutant mice, a decrease of anxiety-like behavior was observed, as measured in the elevated plus-maze, light-dark, and novelty-induced hypophagia tests [112].

Similarly, P2X7R blockade by Brilliant Blue G (BBG) or A-438079 showed antidepressant effects in the UCMS mice model [62, 111]. Under these conditions, the activation of the P2X7R/NLRP3/IL-1β pathway in microglial cells of the mouse hippocampus was observed [111]. BBG also reduced serum TNF-α concentration and depressive-like behavior in mice treated with lipopolysaccharide, an activator of TLR4 [113]. In addition to the behavioral alterations, BBG reversed the UCMS-induced microglial activation and hypothalamic-pituitary-adrenal axis dysregulation [114]. Furthermore, BBG exhibited anti-depressant and anti-anxiety effects in lithium-pilocarpine treated epileptic rats [115]. Non-pharmacological interference with behavioral changes was also reported. Daily electro-acupuncture sessions for 4 weeks significantly attenuated depressive-like behavior caused by UCMS, and this effect was accompanied by a decrease in the expression of P2X7Rs, NLRP3 inflammasome components, and mature IL-1β in the hippocampus [116].

In addition to the microglial P2X7Rs, which cause neuroinflammation and thereby MDD, astroglial P2X7Rs may also be involved in this process. Numerous lines of evidence support the assumption that the modification of astrocytic functions or decreased density of astrocytes in the frontolimbic and hippocampal regions is associated with MDD [117]. It has been reported that a decrease in astrocyte-derived ATP in the medial prefrontal cortex causes depressive-like behavior in mice [118, 119]. Apparently, while ATP is acting *via* P2X2Rs to exert anti-depression, this can be reversed by the adenovirus-mediated silencing of this receptor [118]. Although not confirmed until now, another consequence of a decreased ATP release might be a denervation-like supersensitivity of P2X7Rs to their endogenous agonist ATP, causing depression.

5. BIPOLAR DISORDER AND MANIA

Bipolar disorder is characterized by alternating depressive and manic episodes; the latter disease phase is typically defined by increased psychomotor activity and elevated self-esteem. Similar to MDD, bipolar disorder is also aggregated in families, and epidemiological studies have found evidence for a genetic disposition. However, in this case, a different P2X7R polymorphism (rs1718119 coding for Ala348Thr) was reported to be associated with bipolar disorder [85, 120]. In this disease, the increase in P2X7R-induced IL-1β release and the consequent neuroinflammation suggest a possibly vital therapeutic potential of P2X7R antagonists [121, 122]. It has been recently reported that P2RX7 gene variants show sex-specific effects, and increased P2X7R functions potentially elevate the risk for bipolar disorder in females [123]. In humans, uric acid, a key end product of purine metabolism, may represent a state marker during mania [124].

In an animal model of mania (treatment of mice with D-amphetamine), an apparent lack of responsiveness to this psychostimulant was observed with respect to locomotor activity, when pharmacological blockers of P2X7Rs were applied, or P2X7R KO mice were used [125] (Table **1**). An increase in IL-1β levels in the hippocampus and striatum accompanied the mania-like state. P2X7Rs were suggested to be involved in the amphetamine-induced hyperlocomotion *via* a mechanism depending on the dopaminergic system, because hyperlocomotion was blocked by the P2X7R antagonist BBG [126]. In conclusion, it appeared that a purinergic system imbalance is associated with the D-amphetamine-induced model of mania and that P2X7Rs may represent a promising molecular therapeutic target for bipolar disorder.

6. SCHIZOPHRENIA

Schizophrenia is characterized by distortions in thinking, perception, emotions, language, sense of self, and behavior. Common experiences include hallucinations (hearing voices or seeing things that do not exist) and delusions (fixed, false beliefs). Strong evidence has accumulated that ATP-driven neuroinflammation is associated with microglial activation, and in most cases, astrogliosis develops during schizophrenia [127, 128]. In contrast to MDD and bipolar disorder, in the first approach, the P2RX7 gene was not found to be associated with schizophrenia [129] (but see below).

Table 1. Selected examples of *in vivo* studies investigating the impact of P2X7R signaling on psychiatric diseases.

Model	Strategy	Impact on Behavior	Impact on Stress/Neuroinflammation	References
Major Depression	-	-	-	-
TST, FST, restraint stress, LPS	WT and P2X7$^{-/-}$ mice, BBG	Prolongation of immobility in FST and TST in WT, smaller change in P2X7$^{-/-}$. Same effect on TST and FST after sub-acute, i.p. BBG in WT.	Increase in ACTH/corticosterone in plasma after restraint stress, a smaller increase in P2X7$^{-/-}$. A decrease in sucrose preference in WT is reversed by i.p. BBG or in P2X7$^{-/-}$.	[108, 109]
TST, FST	WT and P2XR7$^{-/-}$ mice	Prolongation of immobility in FST and TST in WT, smaller change in P2X7$^{-/-}$, no effect on spontaneous locomotion in WT.	Not studied	[106]
FST	WT and P2X7$^{-/-}$ mice	Repeated FST for 3 days. No change in immobility on the 1st day, but larger prolongation on the 2nd and 3rd day in WT. No similar change in P2X7$^{-/-}$.	FST increases c-Fos in hippocampus/amygdala in WT, but not in P2X7$^{-/-}$	[110]
Restraint stress, UCMS	WT and NLRP3$^{-/-}$ mice, Sprague-Dawley rat, A-804598	UCMS in WT mice decreases sucrose consumption; in NLRP3$^{-/-}$ mice, there is no similar change. Chronic i.p. A-804598 antagonizes a comparable effect of UCMS on sucrose consumption in rats.	Increase by restraint of eATP, IL-1β, and active NLRP3 in rat hippocampus. Chronic i.p. A-854098 in WT or genetic deletion of NLRP3 reverses UCMS-induced decrease in sucrose consumption.	[98]
LPS	C57BL/6 mouse, BBG	Prolongation of immobility after LPS in TST and FST; attenuation of this effect by a single dose of i.p. BBG.	Increase in serum TNF-α by LPS; attenuation of this effect by i.p. BBG.	[107]
UCMS,	BALB mouse, BBG	Impairment of nest-making behavior; reversal of this effect by chronic BBG.	Increase in microglial activation in cortex and hippocampus.	[114]
Lithium plus pilocarpine-induced epilepsy	Sprague-Dawley rat, BBG	Prolongation of immobility in FST and decreased sucrose consumption after epilepsy. Two doses of i.p. BBG alleviate these symptoms.	Increased P2X7R expression in hippocampus, and its alleviation by i.p. BBG.	[115]
FST	Flinders Sensitive Line (FSL) and Flinders Resistant Line (FRL) rats, A-804598	Prolongation of immobility time of FST in FSL but not FRL rats. Chronic i.p. A-804598 antagonizes this effect.	Increased BDNF in the brain of FSL by FST. Antagonism by subacute i.p. A-804598 of this effect.	[81]
UCMS, FST	Sprague-Dawley rat, BBG, A-438079	Prolongation of immobility in FST by UCMS is antagonized by chronic BBG or A-438079 infusion into the hippocampus.	Increase in eATP, IL-1β, and caspase in the hippocampus by UCMS. Antagonism of these effects by infusion of BBG or A-438079 into the hippocampus.	[116]
UCMS, FST	Wistar rat, BBG	UCMS increases the prolongation of immobility in FST. This effect is antagonized by chronic i.p. BBG.	UCMS increases mRNA for P2X7R, NLRP1, caspase-1, and IL-1β in the prefrontal cortex. All increases are antagonized by BBG.	[152]
UCMS	Sprague-Dawley rat, FST, EA	Prolonged immobility time in FST by UCMS; reversal of this effect by chronic EA but not by sham-EA.	Increased IL-1β mRNA/protein and NLRP3 protein in hippocampus, and this effect is reversed by EA but not sham-EA.	[116]

(Table 1) contd….

Model	Strategy	Impact on Behavior	Impact on Stress/Neuroinflammation	References
Bipolar Disorder, Mania	-	-	-	-
D-Amphetamine	WT and P2X7$^{-/-}$ mouse, A-438079	Hyperlocomotion by acute or chronic amphetamine in WT is attenuated in P2X7$^{-/-}$. i.c.v. A-438079 and BBG antagonize amphetamine effects in WT.	Increase in brain IL-1β and TNF-α by chronic amphetamine; antagonism of this effect by i.c.v. A-438079.	[108, 125, 126]
Schizophrenia	-	-	-	-
Phencyclidine (PCP)	WT and P2X7$^{-/-}$ mice, JNJ-47965567	Hyperlocomotion, stereotype behavior and social withdrawal by PCP in WT; attenuation of hyperlocomotion and stereotype behavior in P2X7$^{-/-}$, but an increase in social interaction. Smilar effects by i.p. JNJ-47965567.	Not studied	[130]
Phencyclidine	BALB mouse, JNJ-47965567	Sub-chronic PCP causes spatial learning/memory impairment and hyperlocomotion. These effects are antagonized by i.p. JNJ-47975567.	Increase in P2X7R mRNA and protein in hippocampus and prefrontal cortex after i.p. JNJ-47975567 to PCP-treated mice	[133]
Maternal Poly(I:C)	Sprague-Dawley rat	Deficits in pre-pulse inhibition and social interaction.	Increase in P2X7R mRNA in nucleus accumbens.	[136]
Autism Spectrum Disorder	-	-	-	-
Maternal Poly(I:C)	C57BL/6 mouse, suramin	Decreased social preference and sensorimotor coordination are normalized by chronic i.p. suramin.	Cerebral synaptosomal P2X7R protein is decreased; suramin treatment normalizes this change.	[142]
Genetic model	FVB (WT) and Fragile X KO mice	Decreased social preference and sensorimotor co-ordination are normalized by chronic i.p. suramin.	Not studied	[143]
Maternal Poly(I:C)	WT and P2X7$^{-/-}$ mice, C57BL/6 mouse	Decreased social preference and repetitive behaviors in WT, but not in P2X7$^{-/-}$ mice. Reversal of these effects by maternal treatment with JNJ-4795567 in C57BL/6 mice.	Increased ATP and IL-6 in fetal brain of WT, but not P2X7$^{-/-}$ mice.	[144]

Abbreviations: BBG, Brilliant Blue G; BDNF, brain-derived neurotropic factor; EA, electro acupuncture; eATP, extracellular ATP; FST, forced swimming test; i.c.v., intracerebroventricular; i.p., intraperitoneal; IL-1, interleukin-1; LPS, lipopolysaccharide; NLRP3 inflammasome, nucleotide-binding, leucine-rich repeat, pyrin domain containing inflammasome; Poly(I:C), polyinosinic: polycytidylic acid; TNF-α, tumor necrosis factor-α; TST, tail suspension test; UCMS, unexpected chronic mild stress; WT, wild-type.

In the phencyclidine-induced schizophrenia model, both genetic deletion and pharmacological inhibition of P2X7Rs alleviated schizophrenia-like behavioral alterations [130] (Table **1**). The medial prefrontal cortex of P2X7R KO animals displayed distinct changes in the neuronal activation pattern and microglial organization around hyperactive neurons [131]. In addition, basal dopamine concentration was shown to be regulated by P2X7Rs in this area of the brain, with consequences on the behavioral phenotype. It should be, however, noted that in the 6-hydroxy-dopamine injected rodent model of Parkinson's disease, P2X7R antagonists reduced the microglial activation, thereby decreasing degeneration of dopaminergic neurons [132]. P2X7Rs located at dopaminergic neurons or microglial cells appeared to be involved in this effect. On the basis of conclusions drawn from the etiology of the neurological illness, Parkinson's disease, a somewhat similar mode of action has been assumed to be involved in the pathogenesis of the psychiatric illness, schizophrenia, both depending on intact dopamine turnover and undisturbed microglial function [131].

Another recent publication also reported the involvement of P2X7Rs in a phencyclidine-induced animal model of schizophrenia [133]. Severe spatial learning and memory impairment in the Morris water maze, as well as hypermotor behavior in the open-field test, was observed in mice after subchronic injection of phencyclidine. The intraperitoneal (i.p.) application of the P2X7R antagonist JNJ-47965567 reversed these behavioral symptoms.

The i.p. injection of double-stranded RNA polyinosynic-polycytidylic acid (poly[I:C]) was administered to pregnant rodents to induce mimicked maternal bacterial or viral infection; a lifelong impact on the offspring was observed in terms of altered neuroimmune modulations [134]. This method was considered to model neurodevelopmental mental disorders, such as autism spectrum disorder (ASD) and schizophrenia [135]. Open field, elevated plus maze, and

FST revealed that prenatal exposure to poly(I:C) led to depression-like behavior in the offspring of pregnant rats [136]. Deficits in pre-pulse inhibition and social interaction as symptoms of a schizophrenia-like state were also observed. An increase in mRNA for constituents of the P2X7R/NF-κB/NLRP3/IL-1β signaling pathway in the nucleus accumbens/pre-frontal cortex was considered as an indication for neuro-inflammation in depression and schizophrenia in relevant areas of the brain. The authors concluded that P2X7Rs were found to be involved in schizophrenia, although the P2X7R-mRNA was increased only in the nucleus accumbens, and their investigations were limited to female juvenile rats.

The NMDA-R antagonist phencyclidine, also known as angel dust, has an abuse potential in humans; it is a dissociative hallucinogenic drug that also causes distorted perceptions and violent behavior. The use of cannabis has been consistently associated with psychotic experiences [137] and psychotic disorders such as schizophrenia [138]. Several studies suggest that genetic predisposition to schizophrenia is associated with higher levels of cannabis use [139]. In support of this hypothesis, in a sample of mentally healthy individuals, the interactions between regular cannabis consumption and genotype with psychotic experiences were analyzed [140]. A SNAP of the P2RX7 gene (rs7958311; R270H) was associated with risk for a high level of psychotic experiences in regular cannabis users. It was concluded that P2RX7 plays a role in vulnerability to develop psychotic symptoms when consuming cannabis and point to a new pathway that can potentially be targeted by recently developed P2X7R antagonists.

7. AUTISM SPECTRUM DISORDER (ASD)

ASD is a common, highly inherited, and heterogenous neurodevelopmental illness characterized by disturbances of social communication and interaction, paresthesia, repetitive behaviors, and varying degrees of mental retardation. Maternal immune activation is a principal environmental risk factor contributing to ASD and can be modeled experimentally by the injection of poly(I:C) to pregnant rodents at vulnerable times [141]. Injection once a week for 8 weeks with suramin, a non-selective P2X/P2YR antagonist, corrected 16 multisystem abnormalities that defined an ASD-like phenotype in this model [142]. These included correction of the core social deficits and sensorimotor coordination disturbances. Similarly, in the Fragile X (Fmr1) knockout mouse model of ASD, disturbances of social behavior, novelty preference, metabolism, and synapse structure were improved by long-lasting treatment with the general purinergic antagonist, suramin [143]. Selective antagonists for P2X7Rs and the use of $P2RX7^{-/-}$ in mice indicated the involvement of this type of receptor. Maternal immune activation of embryonic mice by the injection of poly(I:C) induced proinflammatory cytokine production in maternal plasma and to a lesser extent in the fetal brain [144]. In the offspring, social deficit, sensorimotor impairment, repetitive behaviors, cerebellar Purkinje cell atrophy, and synaptosome destruction were observed. In P2X7R KO mice, all these changes were absent. The effect of the knockdown of P2X7Rs on poly(I:C)-induced changes could also be mimicked by acute blockade of the receptor with specific antagonists. Thus, the genetic deletion of P2X7Rs or their pharmacological antagonists both eliminated the ASD-like symptoms in various animal models of this disease (Table **1**).

More recently, it has been suggested that a defective release of ATP from astrocytes of the medial prefrontal cortex normally acts at the terminals of GABAergic interneurons which innervate layer 5 pyramidal neurons in this area of the brain; this may interfere with social interaction, being a core symptom of ASD [145]. However, another core symptom of the disease, repetitive behaviors, were not improved by applying ATP or its enzymatically stable agonist ATP-γ-S, both activating P2X2Rs localized at the GABAergic nerve terminals. Hence, in contrast to P2X7Rs, P2X2Rs mediated only some but not all symptoms of ASD.

CONCLUSION

The present review discusses the hypothesis that neuroinflammation is an etiological factor of psychiatric disorders; ATP appears to stimulate the P2X7R/NLRP3/Capase-1/IL-1β-pathway as a common cause of several mental illnesses, such as MDD, bipolar disorder, schizophrenia, and ASD. Most of the evidence is based on animal experimentation, although there are also at least three clinical observations indirectly suggesting the causal involvement of P2X7Rs in depression, which are at the top of the ATP-induced neuroinflammatory events [78]. These observations are as follows: (1) MDD is associated with diseases of chronic inflammation [93-103] (see Section 4). (2) On the reverse, patients with MDD reliably exhibit increased levels of peripheral concentrations of C-reactive protein (CRP) and other markers of systemic inflammation, including the cytokines IL-1, IL-6 and TNF-α as well as their soluble receptors/antagonists [104, 146, 147]. (3) Non-steroidal anti-inflammatory drugs, such as celecoxib [148], appear to improve MDD, and anti-cytokines, such as adalimumab, etanercept, and infliximab, all causing statistically significant improvements in depressive symptoms [149, 150]. Furthermore, augmentation therapy with minocycline, which is known to block microglial activation, also improves MDD [151]. In conclusion, we have reasons to be optimistic about brain penetrant P2X7R antagonists as potential therapeutics for psychiatric disorders, although the available evidence needs to be extended and validated by further clinical data.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

This work was funded by a generous grant from 'The Project First-Class Disciplines Development'; CZYHW1901) of the Chengdu University of Traditional Chinese Medicine to Y.T. and P.I. in order to build up "The International Collaborative Centre for Purinergic Signalling," and grants of the State Administration of Foreign Affairs to support the stays of P.I. and P.R. in Chengdu (G20190236012). Financial support from the Innovation Team and Talents Cultivation Program of the National Administration of Traditional Chinese Medicine (ZYYCXTD-D-202003) and Sichuan Science and Technology Program (2019YFH0108, 2022YFH0006) is also gratefully acknowledged.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

We are most grateful to Wen-Jing Ren for drawing our Graphical Abstract Figure.

REFERENCES

[1] Kessler, R.C.; Bromet, E.J. The epidemiology of depression across cultures. *Annu. Rev. Public Health,* **2013**, *34*(1), 119-138. http://dx.doi.org/10.1146/annurev-publhealth-031912-114409 PMID: 23514317

[2] Graeff, F.G.; Zangrossi, H., Jr The dual role of serotonin in defense and the mode of action of antidepressants on generalized anxiety and panic disorders. *Cent. Nerv. Syst. Agents Med. Chem.,* **2010**, *10*(3), 207-217. http://dx.doi.org/10.2174/1871524911006030207 PMID: 20528764

[3] Harmer, C.J.; Goodwin, G.M.; Cowen, P.J. Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. *Br. J. Psychiatry,* **2009**, *195*(2), 102-108. http://dx.doi.org/10.1192/bjp.bp.108.051193 PMID: 19648538

[4] Haapakoski, R.; Ebmeier, K.P.; Alenius, H.; Kivimäki, M. Innate and adaptive immunity in the development of depression: An update on current knowledge and technological advances. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2016**, *66*, 63-72. http://dx.doi.org/10.1016/j.pnpbp.2015.11.012 PMID: 26631274

[5] Pariante, C.M. Neuroscience, mental health and the immune system: Overcoming the brain-mind-body trichotomy. *Epidemiol. Psychiatr. Sci.,* **2016**, *25*(2), 101-105. http://dx.doi.org/10.1017/S204579601500089X PMID: 26503420

[6] Illes, P.; Burnstock, G.; Tang, Y. Astroglia-derived ATP modulates CNS neuronal circuits. *Trends Neurosci.,* **2019**, *42*(12), 885-898. http://dx.doi.org/10.1016/j.tins.2019.09.006 PMID: 31704181

[7] Li, Q.; Barres, B.A. Microglia and macrophages in brain homeostasis and disease. *Nat. Rev. Immunol.,* **2018**, *18*(4), 225-242. http://dx.doi.org/10.1038/nri.2017.125 PMID: 29151590

[8] Rech, J.C.; Bhattacharya, A.; Letavic, M.A.; Savall, B.M. The evolution of P2X7 antagonists with a focus on CNS indications. *Bioorg. Med. Chem. Lett.,* **2016**, *26*(16), 3838-3845. http://dx.doi.org/10.1016/j.bmcl.2016.06.048 PMID: 27426304

[9] Yirmiya, R.; Rimmerman, N.; Reshef, R. Depression as a microglial disease. *Trends Neurosci.,* **2015**, *38*(10), 637-658. http://dx.doi.org/10.1016/j.tins.2015.08.001 PMID: 26442697

[10] Dantzer, R.; O'Connor, J.C.; Freund, G.G.; Johnson, R.W.; Kelley, K.W. From inflammation to sickness and depression: When the immune system subjugates the brain. *Nat. Rev. Neurosci.,* **2008**, *9*(1), 46-56. http://dx.doi.org/10.1038/nrn2297 PMID: 18073775

[11] Kiecolt-Glaser, J.K.; Derry, H.M.; Fagundes, C.P. Inflammation: Depression fans the flames and feasts on the heat. *Am. J. Psychiatry,* **2015**, *172*(11), 1075-1091. http://dx.doi.org/10.1176/appi.ajp.2015.15020152 PMID: 26357876

[12] North, R.A. Molecular physiology of P2X receptors. *Physiol. Rev.,* **2002**, *82*(4), 1013-1067. http://dx.doi.org/10.1152/physrev.00015.2002 PMID: 12270951

[13] Bartlett, R.; Stokes, L.; Sluyter, R. The P2X7 receptor channel: Recent developments and the use of P2X7 antagonists in models of disease. *Pharmacol. Rev.,* **2014**, *66*(3), 638-675. http://dx.doi.org/10.1124/pr.113.008003 PMID: 24928329

[14] Burnstock, G.; Kennedy, C. P2X receptors in health and disease. *Adv. Pharmacol.,* **2011**, *61*, 333-372. http://dx.doi.org/10.1016/B978-0-12-385526-8.00011-4 PMID: 21586364

[15] Surprenant, A.; Rassendren, F.; Kawashima, E.; North, R.A.; Buell, G. The cytolytic P2Z receptor for extracellular ATP identified as a P2X receptor (P2X7). *Science,* **1996**, *272*(5262), 735-738. http://dx.doi.org/10.1126/science.272.5262.735 PMID: 8614837

[16] Sperlágh, B.; Vizi, E.S.; Wirkner, K.; Illes, P. P2X7 receptors in the nervous system. *Prog. Neurobiol.,* **2006**, *78*(6), 327-346. http://dx.doi.org/10.1016/j.pneurobio.2006.03.007 PMID: 16697102

[17] Di Virgilio, F.; Dal Ben, D.; Sarti, A.C.; Giuliani, A.L.; Falzoni, S. The P2X7 receptor in infection and inflammation. *Immunity,* **2017**, *47*(1), 15-31. http://dx.doi.org/10.1016/j.immuni.2017.06.020 PMID: 28723547

[18] Sluyter, R. The P2X7 receptor. *Adv. Exp. Med. Biol.,* **2017**, *1051*, 17-53. http://dx.doi.org/10.1007/5584_2017_59 PMID: 28676924

[19] Costa-Junior, H.M.; Sarmento Vieira, F.; Coutinho-Silva, R. C terminus of the P2X7 receptor: Treasure hunting. *Purinergic Signal.,* **2011**, *7*(1), 7-19. http://dx.doi.org/10.1007/s11302-011-9215-1 PMID: 21484094

[20] Virginio, C.; MacKenzie, A.; North, R. A.; Surprenant, A. Kinetics of cell lysis, dye uptake and permeability changes in cells expressing the rat P2X7 receptor. *J. Physiol.,* **1999**, *519*(Pt 2), 335-346.

[21] Li, M.; Toombes, G.E.; Silberberg, S.D.; Swartz, K.J. Physical basis of apparent pore dilation of ATP-activated P2X receptor channels. *Nat. Neurosci.,* **2015**, *18*(11), 1577-1583. http://dx.doi.org/10.1038/nn.4120 PMID: 26389841

[22] Pippel, A.; Stolz, M.; Woltersdorf, R.; Kless, A.; Schmalzing, G.; Markwardt, F. Localization of the gate and selectivity filter of the full-length P2X7 receptor. *Proc. Natl. Acad. Sci. USA,* **2017**, *114*(11), E2156-E2165. http://dx.doi.org/10.1073/pnas.1610414114 PMID: 28235784

[23] Pelegrin, P.; Surprenant, A. The P2X(7) receptor-pannexin connection to dye uptake and IL-1beta release. *Purinergic Signal.,* **2009**, *5*(2), 129-137. http://dx.doi.org/10.1007/s11302-009-9141-7 PMID: 19212823

[24] Harkat, M.; Peverini, L.; Cerdan, A.H.; Dunning, K.; Beudez, J.; Martz, A.; Calimet, N.; Specht, A.; Cecchini, M.; Chataigneau, T.; Grutter, T. On the permeation of large organic cations through the pore of ATP-gated P2X receptors. *Proc. Natl. Acad. Sci. USA,* **2017**, *114*(19), E3786-E3795. http://dx.doi.org/10.1073/pnas.1701379114 PMID: 28442564

[25] Karasawa, A.; Michalski, K.; Mikhelzon, P.; Kawate, T. The P2X7 receptor forms a dye-permeable pore independent of its intracellular domain but dependent on membrane lipid composition. *eLife,* **2017**, *6*, 6. http://dx.doi.org/10.7554/eLife.31186 PMID: 28920575

[26] Panchin, Y.; Kelmanson, I.; Matz, M.; Lukyanov, K.; Usman, N.; Lukyanov, S. A ubiquitous family of putative gap junction molecules. *Curr. Biol.,* **2000**, *10*(13), R473-R474. http://dx.doi.org/10.1016/S0960-9822(00)00576-5 PMID: 10898987

[27] Adinolfi, E.; Giuliani, A.L.; De Marchi, E.; Pegoraro, A.; Orioli, E.; Di Virgilio, F. The P2X7 receptor: A main player in inflammation. *Biochem. Pharmacol.,* **2018**, *151*, 234-244. http://dx.doi.org/10.1016/j.bcp.2017.12.021 PMID: 29288626

[28] Illes, P.; Rubini, P.; Ulrich, H.; Zhao, Y.; Tang, Y. Regulation of microglial functions by purinergic mechanisms in the healthy and diseased CNS. *Cells,* **2020**, *9*(5), E1108. http://dx.doi.org/10.3390/cells9051108 PMID: 32365642

[29] Gomez Perdiguero, E.; Schulz, C.; Geissmann, F. Development and homeostasis of "resident" myeloid cells: The case of the microglia. *Glia,* **2013**, *61*(1), 112-120. http://dx.doi.org/10.1002/glia.22393 PMID: 22847963

[30] Salter, M.W.; Stevens, B. Microglia emerge as central players in brain disease. *Nat. Med.,* **2017**, *23*(9), 1018-1027. http://dx.doi.org/10.1038/nm.4397 PMID: 28886007

[31] Pellegatti, P.; Falzoni, S.; Pinton, P.; Rizzuto, R.; Di Virgilio, F. A novel recombinant plasma membrane-targeted luciferase reveals a new pathway for ATP secretion. *Mol. Biol. Cell,* **2005**, *16*(8), 3659-3665. http://dx.doi.org/10.1091/mbc.e05-03-0222 PMID: 15944221

[32] Kurashima, Y.; Amiya, T.; Nochi, T.; Fujisawa, K.; Haraguchi, T.; Iba, H.; Tsutsui, H.; Sato, S.; Nakajima, S.; Iijima, H.; Kubo, M.; Kunisawa, J.; Kiyono, H. Extracellular ATP mediates mast cell-dependent intestinal inflammation through P2X7 purinoceptors. *Nat. Commun.,* **2012**, *3*(1), 1034. http://dx.doi.org/10.1038/ncomms2023 PMID: 22948816

[33] Ferrari, D.; La Sala, A.; Chiozzi, P.; Morelli, A.; Falzoni, S.; Girolomoni, G.; Idzko, M.; Dichmann, S.; Norgauer, J.; Di Virgilio, F. The P2 purinergic receptors of human dendritic cells: Identification and coupling to cytokine release. *FASEB J.,* **2000**, *14*(15), 2466-2476. http://dx.doi.org/10.1096/fj.00-0031com PMID: 11099464

[34] Shieh, C.H.; Heinrich, A.; Serchov, T.; van Calker, D.; Biber, K. P2X7-dependent, but differentially regulated release of IL-6, CCL2, and TNF-α in cultured mouse microglia. *Glia,* **2014**, *62*(4), 592-607. http://dx.doi.org/10.1002/glia.22628 PMID: 24470356

[35] Shiratori, M.; Tozaki-Saitoh, H.; Yoshitake, M.; Tsuda, M.; Inoue, K. P2X7 receptor activation induces CXCL2 production in microglia through NFAT and PKC/MAPK pathways. *J. Neurochem.,* **2010**, *114*(3), 810-819. http://dx.doi.org/10.1111/j.1471-4159.2010.06809.x PMID: 20477948

[36] Panenka, W.; Jijon, H.; Herx, L.M.; Armstrong, J.N.; Feighan, D.; Wei, T.; Yong, V.W.; Ransohoff, R.M.; MacVicar, B.A. P2X7-like receptor activation in astrocytes increases chemokine monocyte chemoattractant protein-1 expression *via* mitogen-activated protein kinase. *J. Neurosci.,* **2001**, *21*(18), 7135-7142. http://dx.doi.org/10.1523/JNEUROSCI.21-18-07135.2001 PMID: 11549724

[37] Di Virgilio, F.; Adinolfi, E. Extracellular purines, purinergic receptors and tumor growth. *Oncogene,* **2017**, *36*(3), 293-303. http://dx.doi.org/10.1038/onc.2016.206 PMID: 27321181

[38] Perregaux, D.; Gabel, C.A. Interleukin-1 beta maturation and release in response to ATP and nigericin. Evidence that potassium depletion mediated by these agents is a necessary and common feature of their activity. *J. Biol. Chem.,* **1994**, *269*(21), 15195-15203. http://dx.doi.org/10.1016/S0021-9258(17)36591-2 PMID: 8195155

[39] Ferrari, D.; Villalba, M.; Chiozzi, P.; Falzoni, S.; Ricciardi-Castagnoli, P.; Di Virgilio, F. Mouse microglial cells express a plasma membrane pore gated by extracellular ATP. *J. Immunol.,* **1996**, *156*(4), 1531-1539. PMID: 8568257

[40] Ferrari, D.; Chiozzi, P.; Falzoni, S.; Dal Susino, M.; Melchiorri, L.; Baricordi, O.R.; Di Virgilio, F. Extracellular ATP triggers IL-1 beta release by activating the purinergic P2Z receptor of human macrophages. *J. Immunol.,* **1997**, *159*(3), 1451-1458. PMID: 9233643

[41] Muñoz-Planillo, R.; Kuffa, P.; Martínez-Colón, G.; Smith, B.L.; Rajendiran, T.M.; Núñez, G. K^+ efflux is the common trigger of NLRP3 inflammasome activation by bacterial toxins and particulate matter. *Immunity,* **2013**, *38*(6), 1142-1153. http://dx.doi.org/10.1016/j.immuni.2013.05.016 PMID: 23809161

[42] Franceschini, A.; Capece, M.; Chiozzi, P.; Falzoni, S.; Sanz, J.M.; Sarti, A.C.; Bonora, M.; Pinton, P.; Di Virgilio, F. The P2X7 receptor directly interacts with the NLRP3 inflammasome scaffold protein. *FASEB J.,* **2015**, *29*(6), 2450-2461. http://dx.doi.org/10.1096/fj.14-268714 PMID: 25690658

[43] Verkhratsky, A.; Burnstock, G. Biology of purinergic signalling: Its ancient evolutionary roots, its omnipresence and its multiple functional significance. *BioEssays,* **2014**, *36*(7), 697-705. http://dx.doi.org/10.1002/bies.201400024 PMID: 24782352

[44] Di Virgilio, F. The therapeutic potential of modifying inflammasomes and NOD-like receptors. *Pharmacol. Rev.,* **2013**, *65*(3), 872-905. http://dx.doi.org/10.1124/pr.112.006171 PMID: 23592611

[45] Thornberry, N.A.; Bull, H.G.; Calaycay, J.R.; Chapman, K.T.; Howard, A.D.; Kostura, M.J.; Miller, D.K.; Molineaux, S.M.; Weidner, J.R.; Aunins, J.; Elliston, K.O.; Ayala, J.M.; Casano, F.J.; Chin, J.; Ding, G.J-F.; Egger, L.A.; Gaffney, E.P.; Limjuco, G.; Palyha, O.C.; Raju, S.M.; Rolando, A.M.; Salley, J.P.; Yamin, T-T.; Lee, T.D.; Shively, J.E.; MacCross, M.; Mumford, R.A.; Schmidt, J.A.; Tocci, M.J. A novel heterodimeric cysteine protease is required for interleukin-1 beta processing in monocytes. *Nature,* **1992**, *356*(6372), 768-774. http://dx.doi.org/10.1038/356768a0 PMID: 1574116

[46] Martinon, F.; Burns, K.; Tschopp, J. The inflammasome: A molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. *Mol. Cell,* **2002**, *10*(2), 417-426. http://dx.doi.org/10.1016/S1097-2765(02)00599-3 PMID: 12191486

[47] Ogura, Y.; Sutterwala, F.S.; Flavell, R.A. The inflammasome: First line of the immune response to cell stress. *Cell,* **2006**, *126*(4), 659-662. http://dx.doi.org/10.1016/j.cell.2006.08.002 PMID: 16923387

[48] Minkiewicz, J.; de Rivero Vaccari, J.P.; Keane, R.W. Human astrocytes express a novel NLRP2 inflammasome. *Glia,* **2013**, *61*(7), 1113-1121. http://dx.doi.org/10.1002/glia.22499 PMID: 23625868

[49] Savio, L.E.B.; de Andrade Mello, P.; da Silva, C.G.; Coutinho-Silva, R. The P2X7 receptor in inflammatory diseases: angel or demon? *Front. Pharmacol.,* **2018**, *9*, 52. http://dx.doi.org/10.3389/fphar.2018.00052 PMID: 29467654

[50] Ainscough, J.S.; Frank Gerberick, G.; Zahedi-Nejad, M.; Lopez-Castejon, G.; Brough, D.; Kimber, I.; Dearman, R.J. Dendritic cell IL-1α and IL-1β are polyubiquitinated and degraded by the proteasome. *J. Biol. Chem.,* **2014**, *289*(51), 35582-35592. http://dx.doi.org/10.1074/jbc.M114.595686 PMID: 25371210

[51] Soare, A.Y.; Freeman, T.L.; Min, A.K.; Malik, H.S.; Osota, E.O.; Swartz, T.H. P2RX7 at the host-pathogen interface of infectious diseases. *Microbiol. Mol. Biol. Rev.,* **2021**, *85*(1), e00055-20. http://dx.doi.org/10.1128/MMBR.00055-20 PMID: 33441488

[52] Dubyak, G.R. P2X7 receptor regulation of non-classical secretion from immune effector cells. *Cell. Microbiol.,* **2012**, *14*(11), 1697-1706. http://dx.doi.org/10.1111/cmi.12001 PMID: 22882764

[53] Yang, D.; He, Y.; Muñoz-Planillo, R.; Liu, Q.; Núñez, G. Caspase-11 requires the pannexin-1 channel and the purinergic P2X7 pore to mediate pyroptosis and endotoxic shock. *Immunity,* **2015**, *43*(5), 923-932. http://dx.doi.org/10.1016/j.immuni.2015.10.009 PMID: 26572062

[54] de Gassart, A.; Martinon, F. Pyroptosis: Caspase-11 unlocks the gates of death. *Immunity,* **2015**, *43*(5), 835-837. http://dx.doi.org/10.1016/j.immuni.2015.10.024 PMID: 26588774

[55] Wallach, D.; Kang, T.B. Programmed cell death in immune defense: Knowledge and presumptions. *Immunity,* **2018**, *49*(1), 19-32. http://dx.doi.org/10.1016/j.immuni.2018.06.019 PMID: 30021143

[56] Bergsbaken, T.; Fink, S.L.; Cookson, B.T. Pyroptosis: Host cell death and inflammation. *Nat. Rev. Microbiol.,* **2009**, *7*(2), 99-109. http://dx.doi.org/10.1038/nrmicro2070 PMID: 19148178

[57] Shi, J.; Zhao, Y.; Wang, K.; Shi, X.; Wang, Y.; Huang, H.; Zhuang, Y.; Cai, T.; Wang, F.; Shao, F. Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death. *Nature,* **2015**, *526*(7575), 660-665. http://dx.doi.org/10.1038/nature15514 PMID: 26375003

[58] Irwin, M.R.; Cole, S.W. Reciprocal regulation of the neural and innate immune systems. *Nat. Rev. Immunol.,* **2011**, *11*(9), 625-632. http://dx.doi.org/10.1038/nri3042 PMID: 21818124

[59] Silberstein, S.; Liberman, A.C.; Dos Santos Claro, P.A.; Ugo, M.B.; Deussing, J.M.; Arzt, E. Stress-related brain neuroinflammation impact in depression: Role of the corticotropin-releasing hormone system and P2X7 receptor. *Neuroimmunomodulation,* **2021**, *28*(2), 52-60. http://dx.doi.org/10.1159/000515130 PMID: 33845478

[60] Hodes, G.E.; Kana, V.; Menard, C.; Merad, M.; Russo, S.J. Neuroimmune mechanisms of depression. *Nat. Neurosci.,* **2015**, *18*(10), 1386-1393. http://dx.doi.org/10.1038/nn.4113 PMID: 26404713

[61] Bhattacharya, A.; Biber, K. The microglial ATP-gated ion channel P2X7 as a CNS drug target. *Glia,* **2016**, *64*(10), 1772-1787. http://dx.doi.org/10.1002/glia.23001 PMID: 27219534

[62] Bhattacharya, A.; Jones, D.N.C. Emerging role of the P2X7-NLRP3-IL1β pathway in mood disorders. *Psychoneuroendocrinology,* **2018**, *98*, 95-100. http://dx.doi.org/10.1016/j.psyneuen.2018.08.015 PMID: 30121550

[63] Mondelli, V.; Vernon, A.C.; Turkheimer, F.; Dazzan, P.; Pariante, C.M. Brain microglia in psychiatric disorders. *Lancet Psychiatry,* **2017**, *4*(7), 563-572. http://dx.doi.org/10.1016/S2215-0366(17)30101-3 PMID: 28454915

[64] Franklin, T.C.; Xu, C.; Duman, R.S. Depression and sterile inflammation: Essential role of danger associated molecular patterns. *Brain Behav. Immun.,* **2018**, *72*, 2-13.

http://dx.doi.org/10.1016/j.bbi.2017.10.025 PMID: 29102801

[65] Cheffer, A.; Castillo, A.R.G.; Corrêa-Velloso, J.; Gonçalves, M.C.B.; Naaldijk, Y.; Nascimento, I.C.; Burnstock, G.; Ulrich, H. Purinergic system in psychiatric diseases. *Mol. Psychiatry,* **2018**, *23*(1), 94-106. http://dx.doi.org/10.1038/mp.2017.188 PMID: 28948971

[66] van Kesteren, C.F.; Gremmels, H.; de Witte, L.D.; Hol, E.M.; Van Gool, A.R.; Falkai, P.G.; Kahn, R.S.; Sommer, I.E. Immune involvement in the pathogenesis of schizophrenia: A meta-analysis on postmortem brain studies. *Transl. Psychiatry,* **2017**, *7*(3), e1075. http://dx.doi.org/10.1038/tp.2017.4 PMID: 28350400

[67] Deussing, J.M.; Arzt, E. P2X7 receptor: A potential therapeutic target for depression? *Trends Mol. Med.,* **2018**, *24*(9), 736-747. http://dx.doi.org/10.1016/j.molmed.2018.07.005 PMID: 30093269

[68] De Marchi, E.; Orioli, E.; Dal Ben, D.; Adinolfi, E. P2X7 receptor as a therapeutic target. *Adv. Protein Chem. Struct. Biol.,* **2016**, *104*, 39-79. http://dx.doi.org/10.1016/bs.apcsb.2015.11.004 PMID: 27038372

[69] Chrovian, C.C.; Soyode-Johnson, A.; Peterson, A.A.; Gelin, C.F.; Deng, X.; Dvorak, C.A.; Carruthers, N.I.; Lord, B.; Fraser, I.; Aluisio, L.; Coe, K.J.; Scott, B.; Koudriakova, T.; Schoetens, F.; Sepassi, K.; Gallacher, D.J.; Bhattacharya, A.; Letavic, M.A. A dipolar cycloaddition reaction to access 6-Methyl-4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridines enables the discovery synthesis and preclinical profiling of a P2X7 antagonist clinical candidate. *J. Med. Chem.,* **2018**, *61*(1), 207-223. http://dx.doi.org/10.1021/acs.jmedchem.7b01279 PMID: 29211470

[70] Letavic, M.A.; Savall, B.M.; Allison, B.D.; Aluisio, L.; Andres, J.I.; De Angelis, M.; Ao, H.; Beauchamp, D.A.; Bonaventure, P.; Bryant, S.; Carruthers, N.I.; Ceusters, M.; Coe, K.J.; Dvorak, C.A.; Fraser, I.C.; Gelin, C.F.; Koudriakova, T.; Liang, J.; Lord, B.; Lovenberg, T.W.; Otieno, M.A.; Schoetens, F.; Swanson, D.M.; Wang, Q.; Wickenden, A.D.; Bhattacharya, A. 4-Methyl-6,7-dihydro-4H-triazolo[4,5-c]pyridine-Based P2X7 receptor antagonists: optimization of pharmacokinetic properties leading to the identification of a clinical candidate. *J. Med. Chem.,* **2017**, *60*(11), 4559-4572. http://dx.doi.org/10.1021/acs.jmedchem.7b00408 PMID: 28493698

[71] Eggers, M.; Rühl, F.; Haag, F.; Koch-Nolte, F. Nanobodies as probes to investigate purinergic signaling. *Biochem. Pharmacol.,* **2021**, *187*, 114394. http://dx.doi.org/10.1016/j.bcp.2020.114394 PMID: 33388283

[72] Menzel, S.; Schwarz, N.; Haag, F.; Koch-Nolte, F. Nanobody-based biologics for modulating purinergic signaling in inflammation and immunity. *Front. Pharmacol.,* **2018**, *9*, 266. http://dx.doi.org/10.3389/fphar.2018.00266 PMID: 29636685

[73] Danquah, W.; Meyer-Schwesinger, C.; Rissiek, B.; Pinto, C.; Serracant-Prat, A.; Amadi, M.; Iacenda, D.; Knop, J.H.; Hammel, A.; Bergmann, P.; Schwarz, N.; Assunção, J.; Rotthier, W.; Haag, F.; Tolosa, E.; Bannas, P.; Boué-Grabot, E.; Magnus, T.; Laeremans, T.; Stortelers, C.; Koch-Nolte, F. Nanobodies that block gating of the P2X7 ion channel ameliorate inflammation. *Sci. Transl. Med.,* **2016**, *8*(366), 366ra162. http://dx.doi.org/10.1126/scitranslmed.aaf8463 PMID: 27881823

[74] Wulff, H.; Christophersen, P.; Colussi, P.; Chandy, K.G.; Yarov-Yarovoy, V. Antibodies and venom peptides: New modalities for ion channels. *Nat. Rev. Drug Discov.,* **2019**, *18*(5), 339-357. http://dx.doi.org/10.1038/s41573-019-0013-8 PMID: 30728472

[75] Bhattacharya, A.; Wang, Q.; Ao, H.; Shoblock, J.R.; Lord, B.; Aluisio, L.; Fraser, I.; Nepomuceno, D.; Neff, R.A.; Welty, N.; Lovenberg, T.W.; Bonaventure, P.; Wickenden, A.D.; Letavic, M.A. Pharmacological characterization of a novel centrally permeable P2X7 receptor antagonist: JNJ-47965567. *Br. J. Pharmacol.,* **2013**, *170*(3), 624-640. http://dx.doi.org/10.1111/bph.12314 PMID: 23889535

[76] Lord, B.; Aluisio, L.; Shoblock, J.R.; Neff, R.A.; Varlinskaya, E.I.; Ceusters, M.; Lovenberg, T.W.; Carruthers, N.; Bonaventure, P.; Letavic, M.A.; Deak, T.; Drinkenburg, W.; Bhattacharya, A. Pharmacology of a novel central nervous system-penetrant P2X7 antagonist JNJ-42253432. *J. Pharmacol. Exp. Ther.,* **2014**, *351*(3), 628-641. http://dx.doi.org/10.1124/jpet.114.218487 PMID: 25271258

[77] Bhattacharya, A. Recent advances in CNS P2X7 physiology and pharmacology: Focus on neuropsychiatric disorders. *Front. Pharmacol.,* **2018**, *9*, 30. http://dx.doi.org/10.3389/fphar.2018.00030 PMID: 29449810

[78] Cully, M. Can anti-inflammatory strategies light up the dim depression pipeline? *Nat. Rev. Drug Discov.,* **2020**, *19*(4), 224-225. http://dx.doi.org/10.1038/d41573-020-00049-5 PMID: 32203290

[79] Timmers, M.; Ravenstijn, P.; Xi, L.; Triana-Baltzer, G.; Furey, M.; Van Hemelryck, S.; Biewenga, J.; Ceusters, M.; Bhattacharya, A.; van den Boer, M.; van Nueten, L.; de Boer, P. Clinical pharmacokinetics, pharmacodynamics, safety, and tolerability of JNJ-54175446, a brain permeable P2X7 antagonist, in a randomised single-ascending dose study in healthy participants. *J. Psychopharmacol.,* **2018**, *32*(12), 1341-1350. http://dx.doi.org/10.1177/0269881118800067 PMID: 30260294

[80] Recourt, K.; van der Aart, J.; Jacobs, G.; de Kam, M.; Drevets, W.; van Nueten, L.; Kanhai, K.; Siebenga, P.; Zuiker, R.; Ravenstijn, P.; Timmers, M.; van Gerven, J.; de Boer, P. Characterisation of the pharmacodynamic effects of the P2X7 receptor antagonist JNJ-54175446 using an oral dexamphetamine challenge model in healthy males in a randomised, double-blind, placebo-controlled, multiple ascending dose trial. *J. Psychopharmacol.,* **2020**, *34*(9), 1030-1042. http://dx.doi.org/10.1177/0269881120914206 PMID: 32248747

[81] Ribeiro, D.E.; Roncalho, A.L.; Glaser, T.; Ulrich, H.; Wegener, G.; Joca, S. P2X7 receptor signaling in stress and depression. *Int. J. Mol. Sci.,* **2019**, *20*(11), E2778. http://dx.doi.org/10.3390/ijms20112778 PMID: 31174279

[82] Illes, P.; Verkhratsky, A.; Tang, Y. Pathological ATPergic signaling in major depression and bipolar disorder. *Front. Mol. Neurosci.,* **2020**, *12*, 331. http://dx.doi.org/10.3389/fnmol.2019.00331 PMID: 32076399

[83] Manoli, D.S.; State, M.W. Autism spectrum disorder genetics and the search for pathological mechanisms. *Am. J. Psychiatry,* **2021**, *178*(1), 30-38. http://dx.doi.org/10.1176/appi.ajp.2020.20111608 PMID: 33384012

[84] McQuillin, A.; Bass, N.J.; Choudhury, K.; Puri, V.; Kosmin, M.; Lawrence, J.; Curtis, D.; Gurling, H.M. Case-control studies show that a non-conservative amino-acid change from a glutamine to arginine in the P2RX7 purinergic receptor protein is associated with both bipolar- and unipolar-affective disorders. *Mol. Psychiatry,* **2009**, *14*(6), 614-620. http://dx.doi.org/10.1038/mp.2008.6 PMID: 18268501

[85] Czamara, D.; Müller-Myhsok, B.; Lucae, S. The P2RX7 polymorphism rs2230912 is associated with depression: A meta-analysis. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2018**, *82*, 272-277. http://dx.doi.org/10.1016/j.pnpbp.2017.11.003 PMID: 29122639

[86] Green, E.K.; Grozeva, D.; Raybould, R.; Elvidge, G.; Macgregor, S.; Craig, I.; Farmer, A.; McGuffin, P.; Forty, L.; Jones, L.; Jones, I.; O'Donovan, M.C.; Owen, M.J.; Kirov, G.; Craddock, N. P2RX7: A bipolar and unipolar disorder candidate susceptibility gene? *Am. J. Med. Genet. B. Neuropsychiatr. Genet.,* **2009**, *150B*(8), 1063-1069. http://dx.doi.org/10.1002/ajmg.b.30931 PMID: 19160446

[87] Feng, W.P.; Zhang, B.; Li, W.; Liu, J. Lack of association of P2RX7 gene rs2230912 polymorphism with mood disorders: A meta-analysis. *PLoS One,* **2014**, *9*(2), e88575. http://dx.doi.org/10.1371/journal.pone.0088575 PMID: 24533115

[88] Wray, N.R.; Ripke, S.; Mattheisen, M.; Trzaskowski, M.; Byrne, E.M.; Abdellaoui, A.; Adams, M.J.; Agerbo, E.; Air, T.M.; Andlauer, T.M.F.; Bacanu, S.A.; Bækvad-Hansen, M.; Beekman, A.F.T.; Bigdeli, T.B.; Binder, E.B.; Blackwood, D.R.H.; Bryois, J.; Buttenschøn, H.N.; Bybjerg-Grauholm, J.; Cai, N.; Castelao, E.; Christensen, J.H.; Clarke, T.K.; Coleman, J.I.R.; Colodro-Conde, L.; Couvy-Duchesne, B.; Craddock, N.; Crawford, G.E.; Crowley, C.A.; Dashti, H.S.; Davies, G.; Deary, I.J.; Degenhardt, F.; Derks, E.M.; Direk, N.; Dolan, C.V.; Dunn, E.C.; Eley, T.C.; Eriksson, N.; Escott-Price, V.; Kiadeh, F.H.F.; Finucane, H.K.; Forstner, A.J.; Frank, J.; Gaspar, H.A.; Gill, M.; Giusti-Rodríguez, P.; Goes, F.S.; Gordon, S.D.; Grove, J.; Hall, L.S.; Hannon, E.; Hansen, C.S.; Hansen, T.F.; Herms, S.; Hickie, I.B.; Hoffmann, P.; Homuth, G.; Horn, C.; Hottenga, J.J.; Hougaard, D.M.; Hu, M.; Hyde, C.L.; Ising, M.; Jansen, R.; Jin, F.; Jorgenson, E.; Knowles, J.A.; Kohane, I.S.; Kraft, J.; Kretzschmar, W.W.; Krogh, J.; Kutalik, Z.; Lane, J.M.; Li, Y.; Li, Y.; Lind, P.A.; Liu, X.; Lu, L.; MacIntyre, D.J.; MacKinnon, D.F.; Maier, R.M.; Maier, W.; Marchini, J.;

Mbarek, H.; McGrath, P.; McGuffin, P.; Medland, S.E.; Mehta, D.; Middeldorp, C.M.; Mihailov, E.; Milaneschi, Y.; Milani, L.; Mill, J.; Mondimore, F.M.; Montgomery, G.W.; Mostafavi, S.; Mullins, N.; Nauck, M.; Ng, B.; Nivard, M.G.; Nyholt, D.R.; O'Reilly, P.F.; Oskarsson, H.; Owen, M.J.; Painter, J.N.; Pedersen, C.B.; Pedersen, M.G.; Peterson, R.E.; Pettersson, E.; Peyrot, W.J.; Pistis, G.; Posthuma, D.; Purcell, S.M.; Quiroz, J.A.; Qvist, P.; Rice, J.P.; Riley, B.P.; Rivera, M.; Saeed Mirza, S.; Saxena, R.; Schoevers, R.; Schulte, E.C.; Shen, L.; Shi, J.; Shyn, S.I.; Sigurdsson, E.; Sinnamon, G.B.C.; Smit, J.H.; Smith, D.J.; Stefansson, H.; Steinberg, S.; Stockmeier, C.A.; Streit, F.; Strohmaier, J.; Tansey, K.E.; Teismann, H.; Teumer, A.; Thompson, W.; Thomson, P.A.; Thorgeirsson, T.E.; Tian, C.; Traylor, M.; Treutlein, J.; Trubetskoy, V.; Uitterlinden, A.G.; Umbricht, D.; Van der Auwera, S.; van Hemert, A.M.; Viktorin, A.; Visscher, P.M.; Wang, Y.; Webb, B.T.; Weinsheimer, S.M.; Wellmann, J.; Willemsen, G.; Witt, S.H.; Wu, Y.; Xi, H.S.; Yang, J.; Zhang, F.; Arolt, V.; Baune, B.T.; Berger, K.; Boomsma, D.I.; Cichon, S.; Dannlowski, U.; de Geus, E.C.J.; DePaulo, J.R.; Domenici, E.; Domschke, K.; Esko, T.; Grabe, H.J.; Hamilton, S.P.; Hayward, C.; Heath, A.C.; Hinds, D.A.; Kendler, K.S.; Kloiber, S.; Lewis, G.; Li, Q.S.; Lucae, S.; Madden, P.F.A.; Magnusson, P.K.; Martin, N.G.; McIntosh, A.M.; Metspalu, A.; Mors, O.; Mortensen, P.B.; Müller-Myhsok, B.; Nordentoft, M.; Nöthen, M.M.; O'Donovan, M.C.; Paciga, S.A.; Pedersen, N.L.; Penninx, B.W.J.H.; Perlis, R.H.; Porteous, D.J.; Potash, J.B.; Preisig, M.; Rietschel, M.; Schaefer, C.; Schulze, T.G.; Smoller, J.W.; Stefansson, K.; Tiemeier, H.; Uher, R.; Völzke, H.; Weissman, M.M.; Werge, T.; Winslow, A.R.; Lewis, C.M.; Levinson, D.F.; Breen, G.; Børglum, A.D.; Sullivan, P.F. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat. Genet.,* **2018**, *50*(5), 668-681. http://dx.doi.org/10.1038/s41588-018-0090-3 PMID: 29700475

[89] Gu, B.J.; Zhang, W.; Worthington, R.A.; Sluyter, R.; Dao-Ung, P.; Petrou, S.; Barden, J.A.; Wiley, J.S.A. A Glu-496 to Ala polymorphism leads to loss of function of the human P2X7 receptor. *J. Biol. Chem.,* **2001**, *276*(14), 11135-11142. http://dx.doi.org/10.1074/jbc.M010353200 PMID: 11150303

[90] Roger, S.; Mei, Z.Z.; Baldwin, J.M.; Dong, L.; Bradley, H.; Baldwin, S.A.; Surprenant, A.; Jiang, L.H. Single nucleotide polymorphisms that were identified in affective mood disorders affect ATP-activated P2X7 receptor functions. *J. Psychiatr. Res.,* **2010**, *44*(6), 347-355. http://dx.doi.org/10.1016/j.jpsychires.2009.10.005 PMID: 19931869

[91] Sun, C.; Chu, J.; Singh, S.; Salter, R.D. Identification and characterization of a novel variant of the human P2X(7) receptor resulting in gain of function. *Purinergic Signal.,* **2010**, *6*(1), 31-45. http://dx.doi.org/10.1007/s11302-009-9168-9 PMID: 19838818

[92] Aprile-Garcia, F.; Metzger, M.W.; Paez-Pereda, M.; Stadler, H.; Acuña, M.; Liberman, A.C.; Senin, S.A.; Gerez, J.; Hoijman, E.; Refojo, D.; Mitkovski, M.; Panhuysen, M.; Stühmer, W.; Holsboer, F.; Deussing, J.M.; Arzt, E. Co-expression of wild-type P2X7R with Gln460Arg variant alters receptor function. *PLoS One,* **2016**, *11*(3), e0151862. http://dx.doi.org/10.1371/journal.pone.0151862 PMID: 26986975

[93] Metzger, M.W.; Walser, S.M.; Dedic, N.; Aprile-Garcia, F.; Jakubcakova, V.; Adamczyk, M.; Webb, K.J.; Uhr, M.; Refojo, D.; Schmidt, M.V.; Friess, E.; Steiger, A.; Kimura, M.; Chen, A.; Holsboer, F.; Arzt, E.; Wurst, W.; Deussing, J.M. Heterozygosity for the mood disorder-associated variant Gln460Arg alters P2X7 receptor function and sleep quality. *J. Neurosci.,* **2017**, *37*(48), 11688-11700. http://dx.doi.org/10.1523/JNEUROSCI.3487-16.2017 PMID: 29079688

[94] Monif, M.; Burnstock, G.; Williams, D.A. Microglia: Proliferation and activation driven by the P2X7 receptor. *Int. J. Biochem. Cell Biol.,* **2010**, *42*(11), 1753-1756. http://dx.doi.org/10.1016/j.biocel.2010.06.021 PMID: 20599520

[95] Illes, P.; Khan, T.M.; Rubini, P. Neuronal P2X7 receptors revisited: Do they really exist? *J. Neurosci.,* **2017**, *37*(30), 7049-7062. http://dx.doi.org/10.1523/JNEUROSCI.3103-16.2017 PMID: 28747388

[96] Zhao, Y.F.; Tang, Y.; Illes, P. Astrocytic and oligodendrocytic P2X7 receptors determine neuronal functions in the CNS. *Front. Mol. Neurosci.,* **2021**, *14*, 641570. http://dx.doi.org/10.3389/fnmol.2021.641570 PMID: 33642994

[97] He, Y.; Taylor, N.; Fourgeaud, L.; Bhattacharya, A. The role of microglial P2X7: Modulation of cell death and cytokine release. *J. Neuroinflammation,* **2017**, *14*(1), 135. http://dx.doi.org/10.1186/s12974-017-0904-8 PMID: 28716092

[98] Iwata, M.; Ota, K.T.; Li, X.Y.; Sakaue, F.; Li, N.; Dutheil, S.; Banasr, M.; Duric, V.; Yamanashi, T.; Kaneko, K.; Rasmussen, K.; Glasebrook, A.; Koester, A.; Song, D.; Jones, K.A.; Zorn, S.; Smagin, G.; Duman, R.S. Psychological stress activates the inflammasome *via* release of adenosine triphosphate and stimulation of the purinergic type 2X7 receptor. *Biol. Psychiatry,* **2016**, *80*(1), 12-22. http://dx.doi.org/10.1016/j.biopsych.2015.11.026 PMID: 26831917

[99] Liu, X.; Xie, Z.; Li, S.; He, J.; Cao, S.; Xiao, Z. PRG-1 relieves pain and depressive-like behaviors in rats of bone cancer pain by regulation of dendritic spine in hippocampus. *Int. J. Biol. Sci.,* **2021**, *17*(14), 4005-4020. http://dx.doi.org/10.7150/ijbs.59032 PMID: 34671215

[100] Zou, Y.; Yang, R.; Li, L.; Xu, X.; Liang, S. Purinergic signaling: A potential therapeutic target for depression and chronic pain. *Purinergic Signal.,* **2021**, [online ahead of print] http://dx.doi.org/10.1007/s11302-021-09801-x PMID: 34338957

[101] Eren-Koçak, E.; Dalkara, T. Ion channel dysfunction and neuroinflammation in migraine and depression. *Front. Pharmacol.,* **2021**, *12*, 777607. http://dx.doi.org/10.3389/fphar.2021.777607 PMID: 34858192

[102] Jiang, L.H.; Baldwin, J.M.; Roger, S.; Baldwin, S.A. Insights into the molecular mechanisms underlying mammalian P2X7 receptor functions and contributions in diseases, revealed by structural modeling and single nucleotide polymorphisms. *Front. Pharmacol.,* **2013**, *4*, 55. http://dx.doi.org/10.3389/fphar.2013.00055 PMID: 23675347

[103] Evans, D.L.; Charney, D.S.; Lewis, L.; Golden, R.N.; Gorman, J.M.; Krishnan, K.R.; Nemeroff, C.B.; Bremner, J.D.; Carney, R.M.; Coyne, J.C.; Delong, M.R.; Frasure-Smith, N.; Glassman, A.H.; Gold, P.W.; Grant, I.; Gwyther, L.; Ironson, G.; Johnson, R.L.; Kanner, A.M.; Katon, W.J.; Kaufmann, P.G.; Keefe, F.J.; Ketter, T.; Laughren, T.P.; Leserman, J.; Lyketsos, C.G.; McDonald, W.M.; McEwen, B.S.; Miller, A.H.; Musselman, D.; O'Connor, C.; Petitto, J.M.; Pollock, B.G.; Robinson, R.G.; Roose, S.P.; Rowland, J.; Sheline, Y.; Sheps, D.S.; Simon, G.; Spiegel, D.; Stunkard, A.; Sunderland, T.; Tibbits, P., Jr; Valvo, W.J. Mood disorders in the medically ill: Scientific review and recommendations. *Biol. Psychiatry,* **2005**, *58*(3), 175-189. http://dx.doi.org/10.1016/j.biopsych.2005.05.001 PMID: 16084838

[104] Howren, M.B.; Lamkin, D.M.; Suls, J. Associations of depression with C-reactive protein, IL-1, and IL-6: A meta-analysis. *Psychosom. Med.,* **2009**, *71*(2), 171-186. http://dx.doi.org/10.1097/PSY.0b013e3181907c1b PMID: 19188531

[105] Jimenez-Mateos, E.M.; Smith, J.; Nicke, A.; Engel, T. Regulation of P2X7 receptor expression and function in the brain. *Brain Res. Bull.,* **2019**, *151*, 153-163. http://dx.doi.org/10.1016/j.brainresbull.2018.12.008 PMID: 30593878

[106] Basso, A.M.; Bratcher, N.A.; Harris, R.R.; Jarvis, M.F.; Decker, M.W.; Rueter, L.E. Behavioral profile of P2X7 receptor knockout mice in animal models of depression and anxiety: Relevance for neuropsychiatric disorders. *Behav. Brain Res.,* **2009**, *198*(1), 83-90. http://dx.doi.org/10.1016/j.bbr.2008.10.018 PMID: 18996151

[107] Sperlagh, B.; Csolle, C.; Ando, R.D.; Goloncser, F.; Kittel, A.; Baranyi, M. The role of purinergic signaling in depressive disorders. *Neuropsychopharmacol. Hung.,* **2012**, *14*(4), 231-238. PMID: 23269209

[108] Csölle, C.; Andó, R.D.; Kittel, Á.; Gölöncsér, F.; Baranyi, M.; Soproni, K.; Zelena, D.; Haller, J.; Németh, T.; Mócsai, A.; Sperlágh, B. The absence of P2X7 receptors (P2rx7) on non-haematopoietic cells leads to selective alteration in mood-related behaviour with dysregulated gene expression and stress reactivity in mice. *Int. J. Neuropsychopharmacol.,* **2013**, *16*(1), 213-233. http://dx.doi.org/10.1017/S1461145711001933 PMID: 22243662

[109] Csölle, C.; Baranyi, M.; Zsilla, G.; Kittel, A.; Gölöncsér, F.; Illes, P.; Papp, E.; Vizi, E.S.; Sperlágh, B. Neurochemical changes in the mouse hippocampus underlying the antidepressant effect of genetic deletion of P2X7 receptors. *PLoS One,* **2013**, *8*(6), e66547. http://dx.doi.org/10.1371/journal.pone.0066547 PMID: 23805233

[110] Boucher, A.A.; Arnold, J.C.; Hunt, G.E.; Spiro, A.; Spencer, J.; Brown, C.; McGregor, I.S.; Bennett, M.R.; Kassiou, M. Resilience and reduced c-Fos expression in P2X7 receptor knockout mice exposed to repeated forced swim test. *Neuroscience,* **2011**, *189*, 170-177. http://dx.doi.org/10.1016/j.neuroscience.2011.05.049 PMID: 21664437

[111] Yue, N.; Huang, H.; Zhu, X.; Han, Q.; Wang, Y.; Li, B.; Liu, Q.; Wu, G.; Zhang, Y.; Yu, J. Activation of P2X7 receptor and NLRP3 inflammasome assembly in hippocampal glial cells mediates chronic stress-induced depressive-like behaviors. *J. Neuroinflammation,* **2017**, *14*(1), 102. http://dx.doi.org/10.1186/s12974-017-0865-y PMID: 28486969

[112] Koo, J.W.; Duman, R.S. Interleukin-1 receptor null mutant mice show decreased anxiety-like behavior and enhanced fear memory. *Neurosci. Lett.,* **2009**, *456*(1), 39-43. http://dx.doi.org/10.1016/j.neulet.2009.03.068 PMID: 19429130

[113] Ma, M.; Ren, Q.; Zhang, J.C.; Hashimoto, K. Effects of brilliant blue G on serum tumor necrosis factor-α levels and depression-like behavior in mice after lipopolysaccharide administration. *Clin. Psychopharmacol. Neurosci.,* **2014**, *12*(1), 31-36. http://dx.doi.org/10.9758/cpn.2014.12.1.31 PMID: 24851118

[114] Farooq, R.K.; Tanti, A.; Ainouche, S.; Roger, S.; Belzung, C.; Camus, V. A P2X7 receptor antagonist reverses behavioural alterations, microglial activation and neuroendocrine dysregulation in an unpredictable chronic mild stress (UCMS) model of depression in mice. *Psychoneuroendocrinology,* **2018**, *97*, 120-130. http://dx.doi.org/10.1016/j.psyneuen.2018.07.016 PMID: 30015007

[115] Hong, S.; Xin, Y.; JiaWen, W.; ShuQin, Z.; GuiLian, Z.; HaiQin, W.; Zhen, G.; HongWei, R.; YongNan, L. The P2X7 receptor in activated microglia promotes depression- and anxiety-like behaviors in lithium -pilocarpine induced epileptic rats. *Neurochem. Int.,* **2020**, *138*, 104773. http://dx.doi.org/10.1016/j.neuint.2020.104773 PMID: 32531197

[116] Yue, N.; Li, B.; Yang, L.; Han, Q.Q.; Huang, H.J.; Wang, Y.L.; Wang, J.; Yu, R.; Wu, G.C.; Liu, Q.; Yu, J. Electro-acupuncture alleviates chronic unpredictable stress-induced depressive- and anxiety-like behavior and hippocampal neuroinflammation in rat model of depression. *Front. Mol. Neurosci.,* **2018**, *11*, 149. http://dx.doi.org/10.3389/fnmol.2018.00149 PMID: 29946236

[117] Rial, D.; Lemos, C.; Pinheiro, H.; Duarte, J.M.; Gonçalves, F.Q.; Real, J.I.; Prediger, R.D.; Gonçalves, N.; Gomes, C.A.; Canas, P.M.; Agostinho, P.; Cunha, R.A. Depression as a glial-based synaptic dysfunction. *Front. Cell. Neurosci.,* **2016**, *9*, 521. http://dx.doi.org/10.3389/fncel.2015.00521 PMID: 26834566

[118] Cao, X.; Li, L.P.; Wang, Q.; Wu, Q.; Hu, H.H.; Zhang, M.; Fang, Y.Y.; Zhang, J.; Li, S.J.; Xiong, W.C.; Yan, H.C.; Gao, Y.B.; Liu, J.H.; Li, X.W.; Sun, L.R.; Zeng, Y.N.; Zhu, X.H.; Gao, T.M. Astrocyte-derived ATP modulates depressive-like behaviors. *Nat. Med.,* **2013**, *19*(6), 773-777. http://dx.doi.org/10.1038/nm.3162 PMID: 23644515

[119] Ma, J.; Qi, X.; Yang, C.; Pan, R.; Wang, S.; Wu, J.; Huang, L.; Chen, H.; Cheng, J.; Wu, R.; Liao, Y.; Mao, L.; Wang, F.C.; Wu, Z.; An, J.X.; Wang, Y.; Zhang, X.; Zhang, C.; Yuan, Z. Calhm2 governs astrocytic ATP releasing in the development of depression-like behaviors. *Mol. Psychiatry,* **2018**, *23*(4), 883-891. http://dx.doi.org/10.1038/mp.2017.229 PMID: 29180673

[120] Backlund, L.; Nikamo, P.; Hukic, D.S.; Ek, I.R.; Träskman-Bendz, L.; Landén, M.; Edman, G.; Schalling, M.; Frisén, L.; Osby, U. Cognitive manic symptoms associated with the P2RX7 gene in bipolar disorder. *Bipolar Disord.,* **2011**, *13*(5-6), 500-508. http://dx.doi.org/10.1111/j.1399-5618.2011.00952.x PMID: 22017219

[121] Söderlund, J.; Olsson, S.K.; Samuelsson, M.; Walther-Jallow, L.; Johansson, C.; Erhardt, S.; Landén, M.; Engberg, G. Elevation of cerebrospinal fluid interleukin-1ß in bipolar disorder. *J. Psychiatry Neurosci.,* **2011**, *36*(2), 114-118. http://dx.doi.org/10.1503/jpn.100080 PMID: 21138659

[122] Jones, G.H.; Vecera, C.M.; Pinjari, O.F.; Machado-Vieira, R. Inflammatory signaling mechanisms in bipolar disorder. *J. Biomed. Sci.,* **2021**, *28*(1), 45. http://dx.doi.org/10.1186/s12929-021-00742-6 PMID: 34112182

[123] Winham, S.J.; Bobo, W.V.; Liu, J.; Coombes, B.; Backlund, L.; Frye, M.A.; Biernacka, J.M.; Schalling, M.; Lavebratt, C. Sex-specific effects of gain-of-function P2RX7 variation on bipolar disorder. *J. Affect. Disord.,* **2019**, *245*, 597-601. http://dx.doi.org/10.1016/j.jad.2018.11.007 PMID: 30445384

[124] Salvadore, G.; Viale, C.I.; Luckenbaugh, D.A.; Zanatto, V.C.; Portela, L.V.; Souza, D.O.; Zarate, C.A., Jr; Machado-Vieira, R. Increased uric acid levels in drug-naïve subjects with bipolar disorder during a first manic episode. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2010**, *34*(6), 819-821. http://dx.doi.org/10.1016/j.pnpbp.2010.02.027 PMID: 20206224

[125] Gubert, C.; Fries, G.R.; Pfaffenseller, B.; Ferrari, P.; Coutinho-Silva, R.; Morrone, F.B.; Kapczinski, F.; Battastini, A.M.O. Role of P2X7 receptor in an animal model of mania induced by D-amphetamine. *Mol. Neurobiol.,* **2016**, *53*(1), 611-620. http://dx.doi.org/10.1007/s12035-014-9031-z PMID: 25502294

[126] Gubert, C.; Andrejew, R.; Leite, C.E.; Moritz, C.E.J.; Scholl, J.; Figueiro, F.; Kapczinski, F.; da Silva Magalhães, P.V.; Battastini, A.M.O. P2X7 purinergic receptor is involved in the pathophysiology of mania: A preclinical study. *Mol. Neurobiol.,* **2020**, *57*(3), 1347-1360. http://dx.doi.org/10.1007/s12035-019-01817-0 PMID: 31729632

[127] Laskaris, L.E.; Di Biase, M.A.; Everall, I.; Chana, G.; Christopoulos, A.; Skafidas, E.; Cropley, V.L.; Pantelis, C. Microglial activation and progressive brain changes in schizophrenia. *Br. J. Pharmacol.,* **2016**, *173*(4), 666-680. http://dx.doi.org/10.1111/bph.13364 PMID: 26455353

[128] Tarasov, V.V.; Svistunov, A.A.; Chubarev, V.N.; Sologova, S.S.; Mukhortova, P.; Levushkin, D.; Somasundaram, S.G.; Kirkland, C.E.; Bachurin, S.O.; Aliev, G. Alterations of astrocytes in the context of schizophrenic dementia. *Front. Pharmacol.,* **2020**, *10*, 1612. http://dx.doi.org/10.3389/fphar.2019.01612 PMID: 32116664

[129] Hansen, T.; Jakobsen, K.D.; Fenger, M.; Nielsen, J.; Krane, K.; Fink-Jensen, A.; Lublin, H.; Ullum, H.; Timm, S.; Wang, A.G.; Jørgensen, N.R.; Werge, T. Variation in the purinergic P2RX(7) receptor gene and schizophrenia. *Schizophr. Res.,* **2008**, *104*(1-3), 146-152. http://dx.doi.org/10.1016/j.schres.2008.05.026 PMID: 18614336

[130] Koványi, B.; Csölle, C.; Calovi, S.; Hanuska, A.; Kató, E.; Köles, L.; Bhattacharya, A.; Haller, J.; Sperlágh, B. The role of P2X7 receptors in a rodent PCP-induced schizophrenia model. *Sci. Rep.,* **2016**, *6*(1), 36680. http://dx.doi.org/10.1038/srep36680 PMID: 27824163

[131] Calovi, S.; Mut-Arbona, P.; Tod, P.; Iring, A.; Nicke, A.; Mato, S.; Vizi, E.S.; Tønnesen, J.; Sperlagh, B. P2X7 receptor-dependent layer-specific changes in neuron-microglia reactivity in the prefrontal cortex of a phencyclidine induced mouse model of schizophrenia. *Front. Mol. Neurosci.,* **2020**, *13*, 566251. http://dx.doi.org/10.3389/fnmol.2020.566251 PMID: 33262687

[132] Glaser, T.; Andrejew, R.; Oliveira-Giacomelli, Á.; Ribeiro, D.E.; Bonfim Marques, L.; Ye, Q.; Ren, W.J.; Semyanov, A.; Illes, P.; Tang, Y.; Ulrich, H. Purinergic receptors in basal ganglia diseases: Shared molecular mechanisms between Huntington's and Parkinson's disease. *Neurosci. Bull.,* **2020**, *36*(11), 1299-1314. http://dx.doi.org/10.1007/s12264-020-00582-8 PMID: 33026587

[133] Huang, H.; Zheng, S.; Chen, M.; Xie, L.; Li, Z.; Guo, M.; Wang, J.; Lu, M.; Zhu, X. The potential of the P2X7 receptor as a therapeutic target in a sub-chronic PCP-induced rodent model of schizophrenia. *J. Chem. Neuroanat.,* **2021**, *116*, 101993. http://dx.doi.org/10.1016/j.jchemneu.2021.101993 PMID: 34147620

[134] Solek, C.M.; Farooqi, N.; Verly, M.; Lim, T.K.; Ruthazer, E.S. Maternal immune activation in neurodevelopmental disorders. *Dev. Dyn.,* **2018**, *247*(4), 588-619. http://dx.doi.org/10.1002/dvdy.24612 PMID: 29226543

[135] Murray, K.N.; Edye, M.E.; Manca, M.; Vernon, A.C.; Oladipo, J.M.; Fasolino, V.; Harte, M.K.; Mason, V.; Grayson, B.; McHugh, P.C.; Knuesel, I.; Prinssen, E.P.; Hager, R.; Neill, J.C. Evolution of a maternal immune activation (mIA) model in rats: Early developmental effects. *Brain Behav. Immun.,* **2019**, *75*, 48-59.

http://dx.doi.org/10.1016/j.bbi.2018.09.005 PMID: 30218784

[136] Su, Y.; Lian, J.; Hodgson, J.; Zhang, W.; Deng, C. Prenatal Poly I:C challenge affects behaviors and neurotransmission *via* elevated neuroinflammation responses in female juvenile rats. *Int. J. Neuropsychopharmacol.,* **2022**, *25*(2), 160-171. http://dx.doi.org/10.1093/ijnp/pyab087 PMID: 34893855

[137] van Gastel, W.A.; MacCabe, J.H.; Schubart, C.D.; Vreeker, A.; Tempelaar, W.; Kahn, R.S.; Boks, M.P. Cigarette smoking and cannabis use are equally strongly associated with psychotic-like experiences: A cross-sectional study in 1929 young adults. *Psychol. Med.,* **2013**, *43*(11), 2393-2401. http://dx.doi.org/10.1017/S0033291713000202 PMID: 23414608

[138] Di Forti, M.; Quattrone, D.; Freeman, T.P.; Tripoli, G.; Gayer-Anderson, C.; Quigley, H.; Rodriguez, V.; Jongsma, H.E.; Ferraro, L.; La Cascia, C.; La Barbera, D.; Tarricone, I.; Berardi, D.; Szöke, A.; Arango, C.; Tortelli, A.; Velthorst, E.; Bernardo, M.; Del-Ben, C.M.; Menezes, P.R.; Selten, J.P.; Jones, P.B.; Kirkbride, J.B.; Rutten, B.P.; de Haan, L.; Sham, P.C.; van Os, J.; Lewis, C.M.; Lynskey, M.; Morgan, C.; Murray, R.M.; Amoretti, S.; Arrojo, M.; Baudin, G.; Beards, S.; Bernardo, M.; Bobes, J.; Bonetto, C.; Cabrera, B.; Carracedo, A.; Charpeaud, T.; Costas, J.; Cristofalo, D.; Cuadrado, P.; Díaz-Caneja, C.M.; Ferchiou, A.; Franke, N.; Frijda, F.; García Bernardo, E.; Garcia-Portilla, P.; González, E.; Hubbard, K.; Jamain, S.; Jiménez-López, E.; Leboyer, M.; López Montoya, G.; Lorente-Rovira, E.; Marcelino Loureiro, C.; Marrazzo, G.; Martínez, C.; Matteis, M.; Messchaart, E.; Moltó, M.D.; Nacher, J.; Olmeda, M.S.; Parellada, M.; González Peñas, J.; Pignon, B.; Rapado, M.; Richard, J-R.; Rodríguez Solano, J.J.; Roldán Díaz, L.; Ruggeri, M.; Sáiz, P.A.; Sánchez, E.; Sanjuán, J.; Sartorio, C.; Schürhoff, F.; Seminerio, F.; Shuhama, R.; Sideli, L.; Stilo, S.A.; Termorshuizen, F.; Tosato, S.; Tronche, A-M.; van Dam, D.; van der Ven, E. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): A multicentre case-control study. *Lancet Psychiatry,* **2019**, *6*(5), 427-436. http://dx.doi.org/10.1016/S2215-0366(19)30048-3 PMID: 30902669

[139] Verweij, K.J.; Abdellaoui, A.; Nivard, M.G.; Sainz Cort, A.; Ligthart, L.; Draisma, H.H.; Minică, C.C.; Gillespie, N.A.; Willemsen, G.; Hottenga, J.J.; Boomsma, D.I.; Vink, J.M. Short communication: Genetic association between schizophrenia and cannabis use. *Drug Alcohol Depend.,* **2017**, *171*, 117-121. http://dx.doi.org/10.1016/j.drugalcdep.2016.09.022 PMID: 28086176

[140] Boks, M.P.; He, Y.; Schubart, C.D.; Gastel, W.V.; Elkrief, L.; Huguet, G.; Eijk, K.V.; Vinkers, C.H.; Kahn, R.S.; Paus, T.; Conrod, P.; Hol, E.M.; de Witte, L.D. Cannabinoids and psychotic symptoms: A potential role for a genetic variant in the P2X purinoceptor 7 (P2RX7) gene. *Brain Behav. Immun.,* **2020**, *88*, 573-581. http://dx.doi.org/10.1016/j.bbi.2020.04.051 PMID: 32330591

[141] Patterson, P.H. Modeling autistic features in animals. *Pediatr. Res.,* **2011**, *69*(5 Pt 2), 34R-40R. http://dx.doi.org/10.1203/PDR.0b013e318212b80f PMID: 21289542

[142] Naviaux, R.K.; Zolkipli, Z.; Wang, L.; Nakayama, T.; Naviaux, J.C.; Le, T.P.; Schuchbauer, M.A.; Rogac, M.; Tang, Q.; Dugan, L.L.; Powell, S.B. Antipurinergic therapy corrects the autism-like features in the poly(IC) mouse model. *PLoS One,* **2013**, *8*(3), e57380. http://dx.doi.org/10.1371/journal.pone.0057380 PMID: 23516405

[143] Naviaux, J.C.; Wang, L.; Li, K.; Bright, A.T.; Alaynick, W.A.; Williams, K.R.; Powell, S.B.; Naviaux, R.K. Antipurinergic therapy corrects the autism-like features in the Fragile X (Fmr1 knockout) mouse model. *Mol. Autism,* **2015**, *6*(1), 1. http://dx.doi.org/10.1186/2040-2392-6-1 PMID: 25705365

[144] Horváth, G.; Otrokocsi, L.; Beko, K.; Baranyi, M.; Kittel, Á.; Fritz-Ruenes, P.A.; Sperlágh, B. P2X7 receptors drive poly(I:C) induced autism-like behavior in mice. *J. Neurosci.,* **2019**, *39*(13), 2542-2561. http://dx.doi.org/10.1523/JNEUROSCI.1895-18.2019 PMID: 30683682

[145] Wang, Q.; Kong, Y.; Wu, D.Y.; Liu, J.H.; Jie, W.; You, Q.L.; Huang, L.; Hu, J.; Chu, H.D.; Gao, F.; Hu, N.Y.; Luo, Z.C.; Li, X.W.; Li, S.J.; Wu, Z.F.; Li, Y.L.; Yang, J.M.; Gao, T.M. Impaired calcium signaling in astrocytes modulates autism spectrum disorder-like behaviors in mice. *Nat. Commun.,* **2021**, *12*(1), 3321. http://dx.doi.org/10.1038/s41467-021-23843-0 PMID: 34059669

[146] Orsolini, L.; Pompili, S.; Valenta, S.T.; Salvi, V.; Volpe, U.C. C-reactive protein as a biomarker for major depressive disorder? *Int. J. Mol. Sci.,* **2022**, *23*(3), 1616. http://dx.doi.org/10.3390/ijms23031616 PMID: 35163538

[147] Felger, J.C.; Haroon, E.; Patel, T.A.; Goldsmith, D.R.; Wommack, E.C.; Woolwine, B.J.; Le, N.A.; Feinberg, R.; Tansey, M.G.; Miller, A.H. What does plasma CRP tell us about peripheral and central inflammation in depression? *Mol. Psychiatry,* **2020**, *25*(6), 1301-1311. http://dx.doi.org/10.1038/s41380-018-0096-3 PMID: 29895893

[148] Köhler, O.; Benros, M.E.; Nordentoft, M.; Farkouh, M.E.; Iyengar, R.L.; Mors, O.; Krogh, J. Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: A systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatry,* **2014**, *71*(12), 1381-1391. http://dx.doi.org/10.1001/jamapsychiatry.2014.1611 PMID: 25322082

[149] Raison, C.L.; Rutherford, R.E.; Woolwine, B.J.; Shuo, C.; Schettler, P.; Drake, D.F.; Haroon, E.; Miller, A.H. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: The role of baseline inflammatory biomarkers. *JAMA Psychiatry,* **2013**, *70*(1), 31-41. http://dx.doi.org/10.1001/2013.jamapsychiatry.4 PMID: 22945416

[150] Kappelmann, N.; Lewis, G.; Dantzer, R.; Jones, P.B.; Khandaker, G.M. Antidepressant activity of anti-cytokine treatment: A systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. *Mol. Psychiatry,* **2018**, *23*(2), 335-343. http://dx.doi.org/10.1038/mp.2016.167 PMID: 27752078

[151] Nettis, M.A.; Lombardo, G.; Hastings, C.; Zajkowska, Z.; Mariani, N.; Nikkheslat, N.; Worrell, C.; Enache, D.; McLaughlin, A.; Kose, M.; Sforzini, L.; Bogdanova, A.; Cleare, A.; Young, A.H.; Pariante, C.M.; Mondelli, V. Augmentation therapy with minocycline in treatment-resistant depression patients with low-grade peripheral inflammation: Results from a double-blind randomised clinical trial. *Neuropsychopharmacology,* **2021**, *46*(5), 939-948. http://dx.doi.org/10.1038/s41386-020-00948-6 PMID: 33504955

[152] Aricioglu, F.; Ozkartal, C.S.; Bastaskin, T.; Tüzün, E.; Kandemir, C.; Sirvanci, S.; Kucukali, C.I.; Utkan, T. Antidepressant-like effects induced by chronic blockade of the purinergic 2X7 receptor through inhibition of non-like receptor protein 1 inflammasome in chronic unpredictable mild stress model of depression in rats. *Clin. Psychopharmacol. Neurosci.,* **2019**, *17*(2), 261-272. http://dx.doi.org/10.9758/cpn.2019.17.2.261 PMID: 30905126