Therapeutic Potential of the Purinergic System in Major Depressive Disorder Associated with COVID-19

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Abstract

Neuroinflammation is closely related to the development of depression, since the latter is caused, among other factors, by inflammatory processes, mainly related to the activation of microglia and expression of specific genes, which occurs during the neuroinflammatory process. Thus, COVID-19 is an important risk factor for the development of depression, since in addition to generating the feeling of stress, which also increases the activity of the immune system, it is also the cause of pathological processes and physiological ones that lead to the development of neuroinflammation, microglial activation, gene expression dysfunction and decreased concentration of available serotonin. That said, drugs are being used to combat COVID-19 to reduce the oxidative stress presented in the disease. Thus, tramadol and fluoxetine are highlighted as drugs used, however, although they present some positive results, such as the reduction of pro-inflammatory cytokines, they are also associated with negative effects such as dependence, pulmonary, cardiac and brain impairment. From this, the purinergic system is highlighted in the literature as a possible therapeutic target. This is because its mechanisms are related to the regulation of microglia, astrocytes and the physiology of important neurotransmitters and hormones. Added to this, there is a modulation of inflammatory activity, especially with regard to the P2X7 receptors of this system. The latter is an important target for the treatment of depression and COVID-19, since positive results were obtained through the genetic exclusion of this receptor and the use of selective antagonists.

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Introduction

In 2019, in Wuhan, a province of China, an increase in pneumonia cases was recorded, which was later associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19 (Huang et al. 2020). The negative effects evidenced by the COVID-19 pandemic, which has lasted more than a year, are significant and involve several factors, such as the illness of the population, the public health crisis and the expressive number of deaths. Furthermore, they are closely associated with the development or exacerbation of neuropsychiatric disorders, including depression (Rogers et al. 2020). This disease, according to the World Health Organization (WHO) (Shu and McCauley 2017), is associated with self-deprecat- ing feelings, such as guilt, low self-esteem and sadness, in addition to loss of interest in activities that were once pleasurable, sleep and appetite disorders, fatigue and poor concentration; it can lead to more serious consequences such as suicide.

According to the study by Kesler and Bromet, depression is of severe, recurrent and recurrent quality, which is closely related to life and function elevation, and is associated with an increase in medical morbidity and mortality (Kessler and Bromet 2013; Spijker et al. 2004; Üstün et al. 2004)—in relation to socioeconomic surveys (such as the prevalence of higher and higher lower-middle-income countries). About age of age (AOO), also wide age range, with an initial media in early adulthood. Thus, the course of most countries is significantly defining recurrent income, which is a wide range of secondary study groups, although individual-level association groups are stronger at low-income levels (Kessler and Bromet 2013).

Depression, which includes major depressive disorder (MDD) diagnoses and depressive symptom classifications, affects 4.4% of the world population, totaling approximately 322 million individuals, and it affects the older population in greater proportion, although it also affects children and adolescents, in addition to affecting more women compared to men (Shu and McCauley 2017). The latter is also evidenced in studies that indicate that women are more affected by stress-induced inflammation (Carlessi et al. 2021), and consequently to successful stress depression (Jeon and Kim 2018). Furthermore, depression is one of the most common causes of suicide (788,000 deaths per year), representing 1.5% of the causes of death in the world (Shu and McCauley 2017). This disorder is also associated with psychosocial and functional impairment, in addition to cognitive deficits (Carlessi et al. 2021), impairing the individual’s functionality in their daily lives (Shu and McCauley 2017).

Acute viral infection by SARS-CoV-2 is associated with neurological symptoms, from sensory symptoms such as
Neuroinflammation Present in Depression and Exacerbated by the COVID-19 Cytokine Storm

Neuroinflammation plays a fundamental role in the development of depression, as it is associated with several mechanisms such as the decrease in available serotonin, dysregulation of the Hypothalamic–Pituitary–Adrenal (HPA) axis and alterations in neurogenesis. These processes are triggered and sustained by the increase in inflammatory substances (Troubat et al. 2021), involving several complex pathophysiological processes of the immune and nervous system, such as the activation of microglia, which generates a release of cytokines and chemokines and gene expression that can be determinant for the development of depressive symptoms (Carlessi et al. 2021).

Serotonin (5-hydroxytryptamine, 5-HT) was discovered 60 years ago, however, studies of its biological functions and receptor activity continue to yield new insights of medical relevance. Data on practically all the main organ systems, including the cardiovascular, pulmonary, gastrointestinal (GI) and genitourinary systems, as well as the central nervous system (CNS) are found (Berger et al. 2009). Since it is important in the regulation of practically all brain functions, and dysregulation of the serotonergic system has been implicated in the pathogenesis of many psychiatric and neurological disorders. Thus, serotonin levels have been implicated in sleep regulation, depression, anxiety, aggression, appetite, temperature, sexual behavior and pain sensation (Yohn et al. 2017).

Thinking about the pathophysiology of depression, three distinct hypotheses about the role of serotonin are discussed: the monoamine, neurotrophic and neurogenic hypotheses (Berger et al. 2009). Thus, there is speculation that decreased neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) or decreased adult hippocampal neurogenesis, are respectively involved in the pathophysiology of depression, and that their restoration is critical for therapeutic efficacy of antidepressant treatment. Thus, 5-HT signaling and 5-HT receptors are strongly involved in the regulation of neurotrophic factor levels and adult hippocampal neurogenesis (Yohn et al. 2017).

Also in this regard, stress plays an important role in the development of neuroinflammation and depression, as it increases the activity of the immune system and the consequent release of pro-inflammatory cytokines, which cross the blood–brain barrier and can affect signal patterns brain and antidepressant mechanisms, in addition to causing changes in neurons and atrophy of astrocytes, both in children and adults (Carlessi et al. 2021), also suppressing...
neuroinflammation (Jeon and Kim 2018). In addition, stress also activates the HPA axis by increasing mRNA and releasing corticotrophin-releasing hormone, increasing cortisol release and decreasing the sensitivity of glucocorticoid receptors, leading to negative feedback inhibition and consequent hypercortisolism (Jeon and Kim 2018). Still on chronic stress, it can intensify pro-inflammatory properties of glucocorticoids, thus becoming a risk factor for depression (Troubat et al. 2021).

Stress also acts indirectly through the change of the intestinal microbiota, which also activates the microglia and, due to the connection of the intestine with the immune, endocrine, autonomic and enteric nervous system, several substances and also pathogens can be carried by the bloodstream reaching the brain tissue (Jeon and Kim 2018). In addition, cytokines also interfere in the metabolism of serotonin, since there is an increase in the activation of indoleamine-2,3-dioxygenase (IDO), which metabolizes tryptophan, which is a precursor of serotonin, thus decreasing its availability (Jeon and Kim 2018).

Regarding the relationship between depression and SARS-CoV-2 infection, it is also necessary to understand the mechanisms of the virus. Upon viral entry, SARS-CoV-2 is able to bind to the cell through the binding of the spike protein (S) expressed in its membrane and the angiotensin 2 (ACE2) receptor, aided by the TMPRSS2 protease in its peptidase domain (Wrapp et al. 2020). In addition, studies have indicated that the entry of the virus into the brain tissue becomes more susceptible, since neuronal and glial cells express this protein in significant amounts (Steardo et al. 2020; Li et al. 2020). Therefore, the entry of these viral particles provides the release of a cascade of pro-inflammatory cytokines marked mainly by increased levels of interleukin-6 (IL-6), interleukin-1 (IL-1) and tumor necrosis factor, consequently increasing the expression of c-reactive protein, ferritin and d-dimer (Fotuhi and Meysami 2020).

With infection, in critically ill patients, the uncontrolled inflammatory response becomes cytokine storm syndrome (DiVirgilio and Sarti 2020). Thus, severe pneumonia develops, approaching acute respiratory distress syndrome (ARDS), although it does not meet all the Berlin criteria (Ranieri et al. 2012). Thus, in 50% of severe cases of COVID-19, severe hypoxemia associated with near-normal respiratory system compliance is perceived (Gattinoni et al. 2020a). Loss of pulmonary perfusion control and vasoconstriction may explain this phenomenon present in COVID-19 pneumonia, causing a large ventilation/perfusion mismatch (Gattinoni et al. 2020b). Thus, this clinical picture is the main cause of morbidity and mortality in patients with Covid-19 (Mehta et al. 2020; Ruan et al. 2020). Direct, uncontrolled, virus-mediated activation of lung macrophages is believed to occur, similar to macrophage activation syndrome (MAS). This syndrome can be seen in some rheumatologic diseases, such as systemic juvenile idiopathic arthritis (sJIA), adult Still’s disease, and systemic lupus erythematosus (SLE), although it is debatable whether hyperinflammation in COVID-19 should be considered MAS sensu strictu (Crayne et al. 2019).

These cytokines that were previously associated with a protective factor in the body, when activated in an exacerbated way, lead to damage to the brain tissue, as they increase the permeability of the blood–brain barrier, allowing a greater entry of pathogens and inflammatory factors (Li et al. 2020). In addition, due to the axonal transport mechanism, there is a rapid spread of the virus, as well as cytokines released by infected neurons generate damage to adjacent cells (Li et al. 2020). Still, in relation to IL-6, it is also associated with the development of some symptoms of depression, such as melancholy (Ting et al. 2020). In addition to the cytokine cascade, the entry of the virus into the cell also causes damage to the functioning of mitochondria (Fotuhi and Meysami 2020), which consequently impairs the mechanisms and pathways of signal transduction and neuronal circuits, leading to an exacerbation of stress oxidative and the cytokine cascade already mentioned, which are factors that are related to the development of depression (Allen et al. 2018).

Furthermore, microglia also play a key role in the perpetuation of neuroinflammation, since, according to Alam et al. (2020), even being associated with a protective function to the brain tissue, its excessive activation promotes an increase in the inflammatory process (Steardo et al. 2020), which therefore contributes to the development of neuroinflammation (Yachou et al. 2020) and demyelination of neuronal cells (Fotuhi and Meysami 2020). Findings in a study developed by Virhammar et al. (2021) and Kanberg et al. (2020) corroborate the idea of greater activation of the aforementioned microglia during the infectious process, since an increase in the expression of the transcriptional activator of the glial fibrillary acidic protein (GFAP) was found in patients diagnosed with COVID-19. That said, according to Carlessi et al. (2021), the cytokine cascade and microglial activation are also fundamental factors in the development of depression and, therefore, patients with COVID-19 who present these factors may be risk groups for the development of this neuropsychiatric pathology.

In addition, pneumonia was reported as one of the complications associated with COVID-19, being reported in several studies (Huang et al. 2020; Politi et al. 2020; Steardo and Zorec 2020; Kurizky et al. 2020; Simões et al. 2021) and it may also be associated with the production of pro-inflammatory factors and activation of the microglia. In addition to damage to mitochondria and activation of the promoter region of miRNAs, the latter being essential in the regulation of gene expression during the inflammatory process (Huang et al. 2020). The factor that associates pneumonia with these
findings is mainly the hypoxia caused, since this leads to the activation of mechanisms related to inflammation (Stearo et al. 2020). Furthermore, lymphopenia related to COVID-19 (Chen et al. 2020) can also become one of the factors for the perpetuation of viral load and systemic inflammation, according to Steardo Junior et al. (2020).

Regarding the entry of the virus into the brain tissue, there is evidence that SARS-CoV-2 can use several routes, one of them through nerves such as the olfactory and the vagus nerve, as the latter would explain the gastrointestinal symptoms, respiratory and neurological symptoms of COVID-19. Furthermore, regarding this mechanism, it is known that the intestine is a highly innervated organ, and intestinal infections are related to a high release of pro-inflammatory cytokines (Simões et al. 2021); granulocyte colony-stimulating factor (G-CSF) (Simões et al. 2021); CCL-2, CCL-3 and CCL-5); granulocyte colony-stimulating factor (G-CSF) (Simões et al. 2021). In relation to the cytokine cascade, it also increases the expression of indoleamine 2,3-dioxygenase, which catalyzes the amino acid tryptophan and therefore leads to a decrease in the available concentration of this molecule, which is directly associated with the production of serotonin (Carlessi et al. 2021) and therefore becomes another essential point in the development of depression in individuals diagnosed with COVID-19.

In turn, the feeling of stress that can be caused by hospitalization, physical isolation, loneliness, among other factors resulting from the COVID-19 pandemic, leads to increased secretion of corticotropin releasing hormone (CRH), which will activate the hypothalamic axis -pituitary-adrenal, causing the release of adrenocorticotropic hormone (ACTH) which leads to an exacerbated activation of glucocorticoids (Stearero et al. 2020; Ruan et al. 2020). This process also leads to an expression of stress-related genes, which as mentioned above, are risk factors for the development of psychiatric disorders, such as depression (Li et al. 2020). This process may also be associated with an increase in the IL-6 cytokine due to stress (Ting et al. 2020) (Fig. 1).

Modulation of Neuroinflammation and Oxidative Stress

The pathological process of depression is closely associated with neuroinflammation and an oxidative process in neural tissue. Thus, considering the exacerbation of inflammation in SARS-CoV-2 infection and the increase in serum levels of cytokines, it is possible to establish a relationship between the worsening of the patient's condition. In addition to other complications, such as acute respiratory failure, acute respiratory distress syndrome (ARDS), or multiple organ failure (Liskova and Samec 2021) and severe hypercoagulability due to hyperfibrinogenemia. Although currently no medication has emerged for the effective treatment of the disease, research studies new possibilities to contain compromising symptoms (El-Ashmawy et al. 2021).

While the positive results of the use of monoamines and neuroendocrines are more studied for the treatment of MDD, other methods for minimizing the disease are being considered. Studies show that mitochondria are closely associated with all hypotheses proposed for the pathophysiological cause of depression to date. It is known that the organelles are responsible for the synthesis of energy in the form of adenosine triphosphate (ATP), participating in the processes of apoptosis, autophagy and in neuronal cell signaling, promoting new synaptic connections. Thus, the decrease in energy production decreases neural plasticity and enhances other inflammatory factors, a factor that is evidenced in patients with MDD (Sharma 2019).

As evidenced in patients with untreated depression, the disease is characterized by an increase in pro-inflammatory...
cytokines and neuroinflammation. Thus, the monoaminergic hypothesis, which considers only the low levels of post-synaptic serotonin, is completed by the hypothesis of an association between neuroinflammation, the serotonin pathways, the HPA axis and the amount of glucocorticoids against immune responses (Troubat et al. 2021).

Thus, the activity of the enzymes of the purinergic system is reduced by oxidative stress, so the intracellular metabolism of purines is closely associated with the generation of ROS. Thus, changes in adenosine concentrations increase oxidative stress, given that the nucleoside activates G protein-coupled P1 receptors, which in general, promote the maintenance of redox hemostasis, decreasing the production of reactive oxygen species (ROS) and increasing the antioxidant enzymes (Savio et al. 2021).

Due to the chronic oxidative stress, the set of these factors are deregulated by inflammatory effects by the activation of purinergic receptors in the microglia, according to the excess of ATP (Troubat et al. 2021). P2X7 is a receptor capable of identifying higher levels of extracellular ATP, which has been extensively studied and highlighted for its pharmacological potential for various psychiatric pathologies (Andrejew et al. 2020). This is controlled by ligand-dependent ion channels that, as large amounts of extracellular ATP, are formed non-selective pores, allowing the entry of the virus into the body leads to a storm of pro-inflammatory cytokines, which play a fundamental role in the development and support of neuroinflammation, as they overcome the blood–brain barrier leading to greater entry of pathogens and inflammatory factors into the brain tissue. Cytokines are also responsible for the increased functioning of indoleamine 2,3-dioxygenase, thus decreasing the concentration of available serotonin.
there are studies that demonstrate a decrease in neurotrophic factors such as BDNF. This specific factor provides neuroprotection through mitogen-activated protein kinase (MEK)-Bcl2, which is decreased in individuals with depression by rotenone, which also inhibits mitochondrial complex I. Thus, with reduced BDNF levels, there is a decrease in the bcl-2 dependent pathway, which consequently affects mitochondrial levels, these processes reduce neuronal plasticity and trigger apoptosis. They also affect epigenetic modulations of neuronal plasticity within the cell by decreasing substrates for the formation of S-adenosylmethylion (SAM), provided by the mitochondria (Sharma 2019).

While gene stress directly affects the alteration of gene structures with DNA methylation and histone acetylation, these factors are linked to the function of mitochondria in these processes. The organelle is responsible for providing a carbon used for the remethylation of homocysteine into methionine, a substance that uses S-adenosylmethylion (SAM) for DNA methylation through methyl, folate and other vitamins (Sharma 2019; Stover 2011). However, the possibility of polymorphism in this pathway, given the activity and expression of DNA and histone methyltransferases, can alter chromatin methylation patterns and trigger the development of neuropsychiatric diseases (Stover 2011).

Other studies involving gene expression mediate the fact of different responses to some antidepressants in different individuals. According to research, this is due to the different expression of various microRNAs (miRNAs). As an example, miR-101 is able to disrupt mitochondrial function by reversing the methylation of a PR domain, as well as, with the decrease of ATP, it triggers the process of mitochondrial-dependent apoptosis. Such factors indicate a possibility of using miRNAs as new studies for the treatment of depression (Sharma 2019). Even though the actions performed by mitochondria depend on the nutritional, occupational, metabolism and age of each person (Sharma 2019). The fact that it plays an important role in synaptic strength, disorders related to oxidative stress, synaptic plasticity, neuronal survival and energy metabolism should not be excluded from treatment possibilities for psychiatric disorders (Bansal and Kuhad 2016).

Current Depression and COVID-19 Therapies

Just as depression has different drugs to reduce oxidative stress, in addition to the search for new compromising pathways and new auxiliary substances to minimize damage, the same is happening for the new disease COVID-19. An example of a drug is tramadol, which through studies, has reduced plasma levels of tumor necrosis factor α (TNF-α), a hypocoagulable effect, reduces oxidative stress malondialdehyde by increasing the antioxidant enzymes superoxide dismutase and glutathione peroxidase, has a
cardioprotective effect by decreasing lactate dehydrogenase levels (LDH) and antidepressant activity through the reuptake of serotonin and norepinephrine (El-Ashmawy et al. 2021).

With regard to the increase in inflammatory cytokines IL-6, IL-1, TNF-α and interferon γ given the cytokine storm, which results in ARDS and multiple organ dysfunction in patients with COVID-19, tramadol has good results for these problems. The drug, therefore, can decrease pro-inflammatory cytokines such as IL-6 and TNF-α, without compromising the modulation of IL-2 in antiviral immunity. One should consider the decrease of T cells in patients with COVID-19 (El-Ashmawy et al. 2021). As well, studies correlate the drug as a potent antioxidant. This is because it increases the enzymes superoxide dismutase (SOD) glutathione peroxidase (GPx), which prevent oxidative damage and decrease MDA (based on studies in rats with testicular ischemia–reperfusion damage) (El-Ashmawy et al. 2021; Asghari et al. 2018). Also used as a study drug against depression, tramadol binds to μ opioid receptors and inhibits the reuptake of norepinephrine and serotonin (El-Ashmawy et al. 2021). In a study of postpartum women treated with tramadol, the results showed a significant decrease in the HADS-A and HADS-D scores (hospital anxiety and depression scale, respectively) (Duan et al. 2018).

Another drug studied to minimize the risks of COVID-19 is Fluoxetine, which also acts on the cytokine storm caused by the virus. In a research systematized by gene expression signatures generated, antidepressants such as fluoxetine, paroxetine, bupropion and dexamethasone were used as anti-inflammatory, as well as genetic knockdown signatures of 27 inflammatory genes potentiated in the IL6-mediated cytokine storm to compare the performance of drugs in diseases such as COVID-19. The results between fluoxetine and dexamethasone demonstrate the potential of fluoxetine in the similarity between gene expression signatures between NF-kappaB and IL6ST compared to the steroid, which treats cytokine-induced hyperinflammation, dexamethasone (Creeden et al. 2021).

Thus, when analyzing the role of IL6, it is necessary to consider that it can trigger a pro- and anti-inflammatory role. When IL6R is membrane-bound, it is characterized by an anti-inflammatory role, however, when IL6ST requires a trans-signaling-mediated response. This response requires soluble IL6R (sIL6R) to be able to interact with IL6 and IL6ST proteins. The other factor, fluoxetine-like NF-kappaB has the function of regulating several pro-inflammatory target genes, such as IL6ST (Creeden et al. 2021). Thus, the use of fluoxetine can interrupt the suppression of NF-kappaB/IL6ST inflammatory genes and minimize the cytokine storm, while maintaining the classic anti-inflammatory IL6R. This also concludes that this function is independent of its action on monoaminergic pathways (Creeden et al. 2021).

For the treatment of depression, fluoxetine works as a selective serotonin reuptake inhibitor (SSRI), while it regulates the 5-HT synaptic cleft, that is, it acts as a method for monoaminergic response (Shu et al. 2019). Recent research studies other important roles for drug use, such as the use of COVID-19, as mentioned. In addition, results indicate that fluoxetine improves mitochondrial involvement, increases concentrations of 5-HT and BDNF in the hippocampus (Shu et al. 2019; Zhang et al. 2021). According to the growing search for medications that at least minimize the pathological conditions of patients diagnosed with COVID-19, studies have shown that the use of antidepressants can reduce the levels of intubation and death in these patients. A research sample operated on 577 patients under intensive care conditions, in which antidepressants were used with a mean dosage of 21.6 (SD = 14.1) milligrams equivalent to fluoxetine. The study uses as a valid theoretical basis the explanation that antidepressants can decrease the cytokine storm, the plasma levels of inflammatory mediators, in addition to inhibiting the activity of acid sphingomyelinase which can prevent the infection of epithelial cells with SARS-CoV-2 (Hoertel et al. 2021).

However, even though studies show positive results for possible treatments for COVID-19 and its inflammatory process, medications such as tramadol and fluoxetine can cause problems that do not compensate for the correct answers. While patients affected at the hospital are treated with opioids, its prolonged use, in addition to the possible risk of causing physical and psychological dependence (Minisy et al. 2017), its overdose can cause hypoxemia, leading to cardiopulmonary and neurological complications. Specifically, tramadol can cause respiratory depression which would result in worsening the outcome of COVID-19. As for all other diseases resulting from the disease, the drug can histologically damage the lungs, heart and cerebral cortex, as it increases inflammatory modulation, increasing levels of CRP and TNF-α (Barbosa et al. 2021).

The same harmful and disease-enhancing effect can happen with fluoxetine. Results from preclinical studies confirm that fluoxetine inhibits Na+ and Ca2+ in cardiac channels, which can compromise cardiac function (even more in chronic heart failure) (Ungvari et al. 2019). Thus, patients with COVID-19 in terminal stages with dangerous pathological conditions, with the use of fluoxetine, cardiac risks can be evidenced. As well as, in elderly individuals, its high use inhibits cerebral autoregulation, causing micro brain injuries (Ungvari et al. 2019). Since the new disease mainly affects the elderly, fluoxetine could aggravate the patient’s condition.

Other studies indicate that heavy use of opioids, such as tramadol, can affect brain neurons, altering neuronal function and structure. This happens through oxidative stress in the brain by inhibiting mitochondrial complexes I, III and
IV in electron transfer, with the absence of complex II generating reactive oxygen species. Together, results show that there was a reduction in non-enzymatic antioxidant agents, glutathione, and glutathione peroxidase after the use of tramadol. There are other hypotheses that explain this process by the long-term alteration of tramadol in the insulin signaling pathway in the brain, which also triggers oxidative stress (Ghoneim et al. 2014).

Through studies carried out to understand the increase in nitric oxide, lipid peroxidation and decrease in antioxidant enzymes in testicular tissues caused by tramadol, researchers claim that the drug primarily affects the cytoskeleton. As well, it can increase the mRNA expression of pro-apoptotic receptors in lymphocytes, heart, lung and spleen, from the alteration of proteins that can trigger apoptosis (Ghoneim et al. 2014). Of these proteins, Fas and caspase-3 increased and Bcl-2 decreased.

For fluoxetine treatments, its use can cause bone damage, increasing evidence of fractures, and calcium build-up leading to cell death. Recent research indicates that depending on the inhibition of serotonin reuptake, these free molecules in abundance in the tissues end up negatively affecting the proliferation, differentiation and mineralization phase of ossification during the osteogenic phase of the endochondral, that is, in bone regeneration (Bradaschia-Correa et al. 2017).

The evidenced calcium accumulation ends up directly inhibiting the respiratory chain, decreasing the mitochondrial ATP production. As calcium increases occur, its leakage from the Endoplasmic Reticulum through the transloc- on activates calcium channels through the STIM1 protein, this process leads to mitochondrial calcium accumulation, resulting in cell necrosis (Charles et al. 2017). Likewise, this extravasation of calcium can result in the heart problems already mentioned. In addition, recent research shows that when fluoxetine acts alone, without the help of other drugs, it ends up not showing antidepressant effects (Ma et al. 2016) (Fig. 2).

**Fig. 2** The action of fluoxetine and tramadol in the body. Fluoxetine, even though it aims to inhibit serotonin reuptake, may contribute beyond the monoaminergic pathways. May reduce cytokine storm through regulation of NF-kappaB in pro-inflammatory genes; It can compromise tissue homeostasis, by decreasing serotonin, increasing or decreasing calcium in different cells; in the cardiac channels there is a decrease in Ca2+, compromising its functionality and possibly causing cardiac dysfunction; in bones, it can compromise the phases of proliferation, differentiation and mineralization of ossification, increasing evidence of fractures; accumulation of mitochondrial calcium, resulting in cell necrosis. Tramadol, used as an opioid, even if it increases antioxidant enzymes such as superoxide dismutase (SOD), decreasing the cytokine storm, can result in damage to the body: cause increased oxidative stress by increasing nitric oxide, lipid peroxidation, decreased enzymes antioxidants in testicular tissues, increase the gene expression of pro-apoptotic receptors in lymphocytes, heart, lung and spleen, compromising lung and cardiac tissue; elevate TNF-α levels compromising several tissues and the cerebral cortex.
Modulation of Purinergic Signaling in Major Depressive Disorder Associated with SARS-CoV-2 Infection

The purinergic system is a complex means of intercellular communication, composed of adenosine nucleotides, adenosine nucleoside, respective receptors and enzymes. Initially seen only as an energy molecule, ATP has been highlighted in the literature as the protagonist of several physiological processes, including inflammatory ones (Cheffer et al. 2018; Bartoli et al. 2020a). From this perspective, considering a neuroinflammatory and oxidized scenario, it is necessary to recognize the expression of receptors and the actions that high levels of extracellular ATP can trigger (Savio et al. 2021) (Tables 1, 2).

The purinergic system acts directly on mechanisms related to neurotransmission and neuromodulation through its receptors (Bartoli et al. 2020b) and thus plays an important role in the regulation of psychological functions and consequently in the pathophysiology of disorders such as depression (Bartoli et al. 2020a), and thus it is essential to recognize its mechanisms and processes to elucidate possible treatment targets for depression. Also, extracellular ATP, one of the main components of the purinergic system, is also related to the regulation of the activities of microglia and astrocytes, which has already been evidenced as one of the components of the development of depression, and therefore, dysregulation of this system lead to changes in the

| Table 1 Possible medications to treat depression associated with COVID-19 |
| --- | --- | --- | --- | --- |
| Medicament | Therapeutic function | Results | Clinical use | Reference |
| Fludoxetine | Inhibition of serotonin reuptake receptors | Affect bone regeneration, increasing fractures | Depression | Wan et al. (2018) |
| Fludoxetine | Inhibition of serotonin reuptake receptors | It compromises cardiac function, causes micro brain injuries | COVID-19 and depression | Chen et al. (2020) |
| Tramadol | Opioid | Oxidative stress | COVID-19 | Shenoy (2020) |
| Tramadol | Inhibit the cytokine storm | Increased CRP and TNF-α; histological lesion in the lungs, heart and cerebral cortex | COVID-19 | Simões et al. (2021) |
| Tramadol | Opioid | Respiratory depression | COVID-19 | Ungvari et al. (2019) |

| Table 2 Treatments for depression associated with SARS-CoV-2 infection with P2X7 modulation |
| --- | --- | --- | --- | --- |
| Purinergic component | Therapeutic function | Results | Treatment for | Reference |
| Genetic deletion of P2X7 receptors | Reduction of cytokine storm | Elevation of BDNF and 5-HT in the hippocampus and increased neurogenesis | Depression | Ribeiro et al. (2019) |
| Genetic deletion of P2X7 receptors | Reduction of cytokine storm | Phenotypes with less depressive characteristics and greater ability to adapt to oxidative stress | Depression | Wang and Dwivedi (2017) |
| Genetic deletion of P2X7 receptors | Reduction of cytokine storm | Little increase in 5-HT, BDNF and lack of glutamate release | Depression | Ungvari et al. (2019) |
| AZ-10606120 selective antagonist | Reduction of cytokine storm | Decreased depressive phenotypes | Depression | Ungvari et al. (2019) |
| Blue selective bright G antagonist (BBG) | Reduction of cytokine storm | BDNF increase; decreased GABA and pro-inflammatory cytokines (TNF-α) in microglia in the cortex, hippocampus and basal nuclei | Depression and COVID-19 | Ungvari et al. (2019) |
| JNJ-47965567 and JNJ-42253432 antagonists | Reduction of cytokine storm | Pharmacokinetic potential and brain penetration | Depression and COVID-19 | Ribeiro et al. (2019) |
| Pharmacological inhibition of P2X7R-Panx-1 | Reduction of cytokine storm | Reduction of disseminated depolarization in neuroinflammation | Depression and COVID-19 | Hoertel et al. (2021) |
physiology of neurotransmitters and hormones, also involving the HPA axis (Bartoli et al. 2020a).

With regard to purinergic receptors, they are differentiated into two families: P1 and P2. The P1 are subdivided into A1, A2A, A2B and A3, with the A1 and A3 being activated by adenosine (ADO), and responsible for inhibiting the production of cAMP, while the A2A and A2B stimulate its production (Burnstock 2018). On the other hand, P2 receptors are classified into P2X ionotropic and P2Y metabotropic, and are sensitive to the di (ADP) and triphosphate (ATP) form (Burnstock 2018). Regarding the role of P1 receptors in the central nervous system, A1 and A2A have fundamental functions for the functioning of adenosine in the brain, the first being better distributed in brain tissue while the second is highly expressed in neurons. However, A2B and A3 have limited actions in this regard (Bartoli et al. 2020a).

Furthermore, A1 and A2A receptors are targets of treatment for several psychiatric diseases, as they control synaptic plasticity and release of glutamate, dopamine and GABA, among other neurotransmitters, as well as A3 that regulates the serotonergic and glutamatergic systems (Cheffer et al. 2018). Overall, according to Bartoli et al. (2020a), adenosine induces a negative feedback to the excitatory activities of glutamatergic synapses, acting in neuromodulatory and neuroprotective inhibition. From this, we have that the A1 and A2A receptors exert complementary actions and therefore the release of neurotransmitters depends on a balance between them, since the presynaptic A1 has an inhibitory function in relation to the release of several neurotransmitters, while the Postsynaptic agents reduce neuronal signaling through potassium channels. A2A, on the other hand, seem to be related to the regulation of synaptic plasticity (Bartoli et al. 2020a).

Thus, a non-selective activation of ADO receptors increases the recurrence of depressive symptoms while a selective A2A antagonism or a deletion of these receptors seems to reduce these symptoms. Furthermore, chronic stress can reduce the concentration of available adenosine, thus activating A1 receptors, which as already mentioned, decreases the concentration of available serotonin (Bartoli et al. 2020a), which is related to the development of depressive symptoms (Carlessi et al. 2021) in addition to being related to COVID-19 since it leads to the development of chronic stress in some situations.

Furthermore, depression may also be associated with decreased functionality of astrocytes, which leads to a decreased activation of adenosine 1 inhibitory receptors in neurons, which therefore increases the functioning of A2A receptors, which are associated with neuroplasticity and neuroinflammation it is also associated with suicidal ideation and attempts (Bartoli et al. 2020a), since there is a decrease in adenosine deaminase activity, generating a reduction in adenosine turnover, consequently leading to a decrease in uric acid, which has already been associated to depressive disorders (Bartoli et al. 2020b).

The purinergic system is related to depression, among the factors mentioned, also because the mechanisms of the HPA axis and hormone release are controlled by adenosine receptors, and both A2A and A2B generate an increase in adrenal corticosterone synthesis, in addition to altering the functioning of glucocorticoids (Chen et al. 2010). In addition, adenosine and ATP regulate the activities of microglia and astrocytes, especially with regard to communication between them (Cheffer et al. 2018), which is essential to establish a link with the development of depression, since that the hypoxactivity of astrocytes and the hyperactivation of glia were already mentioned as fundamental factors in the development of depressive disorders (Carlessi et al. 2021).

Regarding P2 receptors, the most studied receptor linked to depression is P2X7, as it is involved in the modulation of different neurotransmitters and pro-inflammatory activity, and in relation to the latter, it is evident that the feeling of stress can influence the mechanisms of the immune system through this receptor (Bartoli et al. 2020a), and thus these receptors have an important role in relation to the neuro-pathology of depression and the purinergic system since it is activated by high concentrations of ATP. Furthermore, the activation of P2X7 leads to an activation of microglia and consequent release of a cascade of pro-inflammatory cytokines, mainly interleukin-1beta (Vereczkei et al. 2019), which leads to changes related to synaptic plasticity, neurogenesis and neuroprotection (Cheffer et al. 2018), becoming an important treatment target in depression since it, as mentioned above, also involves important pro-inflammatory processes. Still, in relation to P2 receptors in general, the combination of non-specific P2 receptor antagonists with antidepressants was associated with positive effects (Bartoli et al. 2020a).

From this, recent researches report the success of adenosine administration and the regulation of ATP release in the treatment of depressive illnesses (Illes et al. 2020a; Gomes et al. 2021). As hypothesized to link mitochondrial function with neuroinflammation that leads to depression, dysfunction of exogenous ATP levels can trigger neuropsychiatric diseases. This happens because stress ends up releasing ATP, which stimulates P2X7 receptors that lead to the release of IL-1β (Sharma 2019), this pre-inflammation factor releases CRH and the active form of the inflammasome of NLRP3 in the hippocampus (Illes et al. 2020a). Thus, recent research studies the genetic inhibition of the P2X7R-Pannexin 1 (Panx-1) pore complex, the suppression of active splice variants of the receptor, using both non-selective P2X7R antagonists and Brilliant Blue G (BBG), antagonist selective for P2X7R, with a potential use for antidepressant treatments (Illes et al. 2020a).
In analyzes carried out in rodents, in which the P2X7Rs genes were removed, the result showed antidepressant phenotypes, related to mood behavior. In other words, the absence of P2X7R, which could be pharmacologically induced, could act as an antidepressant. An example of pharmacological use is P2X7R Brilliant Blue G, performed in the same genetic suppression research, which neutralized the depressive behavior of mice induced by bacterial endotoxin (Savio et al. 2018).

From a negative perspective of the use of this treatment, studies indicate that ATP blockade and evidence of the use of lower extracellular concentrations do not result in the action of the antagonist. There are problems that hinder the action of this antagonist, in addition to the fact that it only acts at high concentrations of ATP, current research has used rodent receptors as experimental use when investigated in human receptors in vitro, the result was not the same. In addition, P2X7R antagonists do not have easy permeability to the CNS, as they must pass through the blood–brain barrier (Illes et al. 2020a). However, several current researches demonstrate drugs that achieved excellent penetration in the cerebral cortex of rodents, when administered subcutaneously (Illes et al. 2020a). As an example of potent P2X7R antagonists, there is AZ-10606120 (Csölle et al. 2013), JNJ-47965567 and JNJ-42253432 (Illes et al. 2020a).

It is known that stressful situations cause an increase in exogenous ATP in the brain, activating P2X7Rs receptors which then release IL-1β and NLRP3, increasing the levels of glucocorticoids and adrenocorticotropic hormone. While such factors were evidenced in patients with TMD, microglia becomes an important agent and target of studies in this disorder. This is because it participates in the tripartite synapse (which occurs between pre and post ganglion cells and astrocytes) which is regulated according to the levels of ATP, related to its P2X and P2Y receptors (Illes et al. 2020a). Microglia can, therefore, carry out cell proliferation or apoptosis, depending on the receptors and levels of ATP. The P2X7 receptor showed to perform apoptosis even in the absence of ATP, while others such as P2Y1Rs coordinate the migration of microglia and P2Y6Rs guide the phagocytosis of bacteria and cell debris. The P2X7 ends up affecting the microglia through signal transduction pathways leading to neuroinflammation, as the release of cytokines, reactive oxygen and nitrogen species that can generate depressive reactions (Illes et al. 2020a).

In comparison with the monoaminergic proposal for the treatment of depression, the P2X7 receptor can also modulate the release of 5-HT, norepinephrine and glutamate. Even though recent research does not know the exact location of the receptor given the lack of selective drugs to recognize its subtype, there are contradictions between current findings. While there is evidence that P2X7R knockout mice showed high levels of 5-HT in the hippocampus under stressful circumstances, acting in monoaminergic upregulation, as well as evidence from genetically deficient mice in the receptor, there is a decrease in the release of 5-HT in the hippocampus, it can also happen to inhibit 5-HT and noradrenaline, impairing depressive behavior (Ribeiro et al. 2019).

There are also different perspectives regarding the relationship between the receptor and the release of GABA. While research demonstrates that P2X7R stimulation in the hippocampus induces glutamate release, inhibition of the receptors can also release GABA through adenosine hydrolysis. Likewise, in astrocyte cultures, P2X7R reduces the expression of the sodium-dependent glutamate/aspartate transporter (GLAST) decreasing GABA and glutamate uptake in rat experiments. As well as it can affect the formation of nitric oxide according to situations of oxidative stress through the stimulation of P2X7R. From the use of receptor antagonists as antidepressant treatment, there was a decrease in NO in the prefrontal cortex of mice. That is, P2X7R can also increase NO concentrations in the limbic regions of the brain and the use of antagonists can be used as antidepressants (Ribeiro et al. 2019).

For adenosine reception by the purinergic system, there are the P1 family receptors, which have different actions in the regulation of depressive symptoms. While A1Rs have antidepressant and anxiolytic properties, A2ARs have opposite effects and their antagonism leads to antidepressant effects. This is regulated according to the level of adenosine administered, and at a higher level, the more chances of achieving a positive effect in the treatment (Gomes et al. 2021). Different researches carried out on the genetic encodings of the A1R receptor still have divergences in their conclusions about the effects of the receptor, although there is no evidence about its effective functioning in the brain of humans with MDD. Research involving depressive disorder is induced in rats by different stressful situations, thus, there are different reports on the actions of the receptor. Although some studies demonstrate that stress decreases A1R levels in the hippocampus, others show an increase in the levels of A1R-binding protein in the hippocampus (Gomes et al. 2021).

Thus, even without obtaining a definitive answer about the action of the variation in A1R levels, agonists, antagonists and the deletion on the receptor were studied. A1R agonists potentiate antidepressant effects, reducing behavioral stress situations in rats, both in doses with zinc and in weekly doses. However, the action of an antagonist on the receptor does not demonstrate antidepressant behavioral effects, only blocking adenosine’s antidepressant effects. A1R deletion increased the effects of behavioral stress, while overexpression deleted these behaviors and stimulated antidepressant habits. However, there are studies that
demonstrate that the effects of this overexpression can vary in different places in the brain (Gomes et al. 2021).

However, higher levels of A2AR demonstrate states of stress and depressive behavior in research with rats. However, other research demonstrates that the ADORA2A gene responsible for encoding the receptor is related to greater resilience to depression, and improvement in common depression behaviors. Other research concludes that there is no correlation between the gene and depressive disorder. Furthermore, there are researches that by genetically overexpressing the A2AR receptor in human neurons, they confirm phenotypes similar to depression (Gomes et al. 2021).

There is significant scientific evidence supporting the action of A2AR antagonists on positive outcomes for common depression phenotypes, while decreasing dopaminergic depolarization. This ability may be related to the concomitant action of other receptor antagonists (such as KW6002 or SCH58261), which together reduced the oxidative stress in the hippocampus, according to postpartum TDM data. In other researches, the use of A2AR antagonists demonstrate resilience to synaptic plasticity and oxidative stress (Gomes et al. 2021).

As in depression, symptoms added to COVID-19 result in greater release of ATP/ADP, stimulating the purinergic system and the actions already described. Thus, the purinergic system and the activation of purinergic receptors can aggravate some neurodegenerative, thrombolytic and platelet symptoms when associated with COVID-19. The formulation of thromboinflammation, in addition to being regulated by thrombin (PAR) signaling and platelet activation, can also be stimulated according to activation of purinergic receptors. From the increase in ATP/ADP, platelet activation causes thrombin to activate fibrinogen, generating fibrin and aggravating conditions willing to formulate thrombi and pro-inflammatory factors. While pulmonary inflammation also releases greater amounts of adenosine and ATP, patients with COVID-19 are more likely to develop thrombosis upon purinergic activation. P2Y1 and P2Y2 receptors were studied for the production of nitric oxide (antithrombotic factor), decreased tissue permeability, and oxidative stress from their inhibitions. Like other adrenergic receptors/ATP, P2Y6 is involved in lung injuries, as well as influences inflammatory conditions as well as P2X7 (Sriram and Insel 2021).

Currently, several studies are studying the potential of antagonism or deletion of the P2X7 receptor as a possible

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**Fig. 3** Outline of the proposal of the P2X7 receptor as a modulator of the consequences of the cytokine cascade. Proposed therapeutic scheme to stabilize the consequences of increased ATP/Ado when evidenced by oxidative stress and cytokine storm. As Ado receptors involved in depression and neuroinflammation, A1R and A2AR are responsible for controlling synaptic plasticity and releasing several neurotransmitters, including a decrease in available serotonin. Furthermore, the A2AR receptor is also related to suicide attempts precisely because of its potential for neuroplasticity and neuroinflammation. As the ATP receptor involved in depression and neuroinflammation, there is P2X7, which can increase the concentration of pro-inflammatory cytokines (IL-1β and TNF-α), and consequently lead to the development of depressive disorder and COVID-19 morbidity. As a therapeutic potential, there is the P2X7 antagonist, which by blocking this receptor, reduces the cytokine storm, increases 5HT and BDNF, reducing depressive phenotypes, which may reduce depression.
option for reducing the symptoms of COVID-19. There is evidence of its role in inflammatory diseases, sepsis, acute/chronic infections, lung and brain inflammation, in which the receptor ends up stimulating and aggravating these factors because it is linked to inflammation pathways (Ribeiro et al. 2019). Thus, since these symptoms are evidenced in patients with COVID-19, as well as mediated by the same inflammatory pathway in depression, purinergic control as a treatment for such pathologies can be a positive hypothesis to avoid psychiatric disorders and inflammatory diseases, such as SARS-CoV-2 infection (Fig. 3).

**Future Proposals**

There are theories that try to correlate P2X7 with BDNF functionality as joint factors in the modulation of neuronal plasticity. While researches that block the receptor identify the increase in BDNF and decrease in depressive behaviors in the hippocampus. Therefore, following this line of research that concerns comparing the receptor to depressive activities in mice, many confirm the increase in P2X7 in animals in vivo exposed to mild unpredictable chronic stress (CUMS). The increase in the receptor varies in amount and brain region (hippocampus or medial prefrontal cortex) depending on the type of stress manifested. Likewise, the absence of the receptor results in phenotypes with less depressive characteristics and greater capacity to adapt to oxidative stress (Ribeiro et al. 2019).

Other researchers showed the same results when correlating P2X7 and depression. When studying P2X7R −/− mice, there was an increase in BDNF, an increase in 5-HT in the hippocampus and greater neurogenesis (Illes et al. 2020a). Thus, it is concluded that the receptor may be linked with depression, following the reasoning already described, in which excessive stress produces glutamate, which secretes large amounts of ATP, activating receptors that then stimulate higher pro-inflammatory levels in the brain, strictly linked to the biochemical symptoms of depression, aggravating or stimulating the disease (Wang et al. 2020a).

Therefore, researches demonstrate the potential between the genetic exclusion of the receptor, or selective antagonists, with the purpose of a new pharmacological method to minimize depression and neuroinflammation. Based on studies that correlated genetic deletion and the use of receptor antagonists with depressive phenotypes, glutamate, BDNF and 5-HT levels in the mouse hippocampus, P2X7R results in a significant difference in the results. In this, wild type P2X7R +/+ (overexpressed) and P2X7R −/− (genetically deleted), AZ-10606120 (Gölöncsér et al. 2017) and selective P2X7R Bright Blue G (BBG) type antagonists (Csölle et al. 2013) were used.

The results found were significant compared to the monoaminergic antidepressant “citalopram” used. The antagonist AZ-10606120 in P2X7R +/+ mice decreased much greater depressive effects compared to the drug compared, as well as the antagonist decreased anhedonia (Csölle et al. 2013). However, another study identified that the same antagonist can significantly decrease the release of [3H] 5-HT by electrical and optical stimulation (Gölöncsér et al. 2017). BBG also decreases depressive behaviors in addition to significantly increasing hippocampal BDNF levels in P2X7R +/+ and P2X7R −/− mice reversing negative levels of the receptor agonist (Csölle et al. 2013) also reduced GABA release (Ribeiro et al. 2019). Treatment with BBG also decreased the increase in pro-inflammatory cytokines such as TNF-α, in microglia in the cortex, hippocampus and basal nuclei of mice (Ribeiro et al. 2019). However, the selective antagonist P2X7R Bright G blue did not affect the residual amount of Glutamate in P2rx7 −/− mice (Csölle et al. 2013).

The genetic deletion of P2X7 is also studied as one of the hypotheses for depressive treatment, even though it does not show many results as the use of antagonists. The deletion expressed in the same previous research, by P2X7 −/− mice, generate behavioral results similar to P2X7 +/+, or with little significant difference. The results identified were increased levels of 5-HT, BDNF and lack of glutamate release. However, even though antidepressant phenotypes were evidenced in mice with receptor deletion, selective antagonists had better antidepressant outcomes (Csölle et al. 2013).

In correlation to the genetic deletion and the levels of GABA and glutamate, it is evidenced that in its stimulation, the P2X7 can increase these neurotransmitters and decreases their uptake, which elevates depressive and stress factors (Ribeiro et al. 2019). As well as modulating levels of nitric oxide (NO) synthesis in the prefrontal cortex and hippocampus, which induces antidepressant effects (Joca et al. 2019).

In addition to these strategies and conditions included in the set, there is the importance of the correlation between P2X7, NLRP3, depression and COVID-19, which are linked by inflammatory factors. As mentioned, receptor activation triggers the inflammasome effect and all pro-inflammatory cytokines, leading to depression and pathologies associated with COVID-19. Therefore, antagonists or P2X7 deletion can inhibit NLRP3 formation and inflammatory effects on microglial cells (Wang et al. 2020b). Therefore, there are studies that study the pharmacological inhibition of the suppressed P2X7R-Panx-1 pore complex, to decrease depolarization and thus neurological inflammation (Illes et al. 2020b; Chen et al. 2017). The activation of NLRP3 in depression and COVID-19-associated pathologies is due to a decrease in the intracellular K⁺ concentration due to the P2X7Rs. In addition to cytokines, damage to the blood–brain barrier
can occur in both diseases, minimized by receptor antagonists. In patients with COVID-19, damage to the barrier caused ischemic stroke, given excessive clots in the lung formed by inflammation. Thus, patients suffering from psychological illnesses such as depression can worsen, or even in other cases, develop the disease more easily (Andrejew et al. 2020).

Following the information about the storm of inflammatory cytokines associated with COVID-19, it is also worth considering the proposal of antagonism or deletion of P2X7 for the treatment of the disease (Andrejew et al. 2020). Recent research shares the same reasoning in search of treatment for severe pneumonia, in favor of preventing pulmonary fibrosis and adverse effects precisely, in search of treatment for severe pneumonia, in favor of preventing pulmonary fibrosis and adverse effects of ventilation (DiVirgilio and Sarti 2020). However, the results have not yet been published, although other institutions recognize the importance of considering the purinergic system and the P2X7 receptor as a possible immediate treatment of the disease (Simões et al. 2021).

**Conclusion**

In view of the different studies discussed, it is possible to see that the connection between depressive disorder and COVID-19 is established as an increase in adenosine and exogenous ATP/ADP, forming the storm of inflammatory cytokines, which result in neuroinflammation, neurodegeneration, among other factors characteristic of every pathology already mentioned. The studies mentioned consider the purinergic system as a therapeutic potential for both depression and COVID-19, as the inhibition of the increase in adenosine and ATP/ADP that influence the secreted inflammatory cytokines. The present study specifically considers the P2X7 purinergic receptor as a therapeutic target, establishing positive results in its genetic deletion or through selective antagonists, which may be promising to minimize the symptoms of COVID-19 and for the treatment of depressive disorder.

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**Data Availability** Enquiries about data availability should be directed to the authors.

**Declarations**

**Conflict of interest** The authors have not disclosed any competing interests.

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