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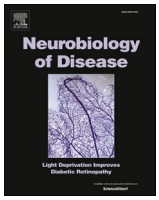

Review

Purinergic receptors in cognitive disturbances

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ABSTRACT

Purinergic receptors (Rs) of the ATP/ADP, UTP/UDP (P2X, P2Y) and adenosine (A1, A2A)-sensitive classes broadly interfere with cognitive processes both under *quasi* normal and disease conditions. During neurodegenerative illnesses, high concentrations of ATP are released from the damaged neuronal and non-neuronal cells of the brain; then, this ATP is enzymatically degraded to adenosine. Thus, the primary injury in neurodegenerative diseases appears to be caused by various protein aggregates on which a superimposed damage mediated by especially P2X7 and A2AR activation develops; this can be efficiently prevented by small molecular antagonists in animal models of the above diseases, or are mitigated in the respective knockout mice. Dementia is a leading symptom in Alzheimer's disease (AD), and accompanies Parkinson's disease (PD) and Huntington's disease (HD), especially in the advanced states of these illnesses. Animal experimentation suggests that P2X7 and A2ARs are also involved in a number of psychiatric diseases, such as major depressive disorder (MDD), obsessive compulsive behavior, and attention deficit hyperactivity disorder. In conclusion, small molecular antagonists of purinergic receptors are expected to supply us in the future with pharmaceuticals which are able to combat in a range of neurological/psychiatric diseases the accompanying cognitive deterioration.

1. Introduction

ATP, originally recognized as a molecule to store energy within cells, was discovered and characterized by Geoffrey Burnstock as an extracellular signaling molecule co-ordinating cellular functions in animals/humans (Burnstock and Knight, 2004; Burnstock, 2012; Burnstock, 2014). Receptors (Rs) which are targets for purine and pyrimidine nucleotides have been classified into two types, the ligand-gated cationic channels P2X (seven mammalian subtypes: P2X1–7) and the G-protein-coupled P2YRs (eight mammalian subtypes: P2Y1, 2, 4, 6, 11–14) (Burnstock and Kennedy, 1985; North, 2002; Illes et al., 2021; Jacobson et al., 2020). The enzymatic degradation product of ATP, adenosine may act at all four types of P1 receptors, termed A1, A2A, A2B and A3 (Fredholm et al., 2011; IJzerman et al., 2022).

ATP was recognized as a (co)transmitter in the peripheral and central nervous system released from neurons (Burnstock, 1976); in addition it has been found to be outpoured into the extracellular space also from all non-neuronal constituents of the CNS (e.g. astrocytes, oligodendrocytes, microglia) by various mechanisms, modulating neuronal activity (Butt, 2011; Illes et al., 2019b; Agostinho et al., 2020; Di Virgilio et al., 2023). In contrast to extensive knowledge gathered on the cellular and molecular actions of nucleotides/nucleosides in nervous tissue, investigations on behavioral consequences of these effects are much less abundant. Our aim was to cast a view on cognition, as the highest order

Abbreviations: AD, Alzheimer's disease; APP, β-amyloid precursor protein; Aβ, β-amyloid; BBG, Brilliant Blue G; CA1, hippocampal CA1 pyramidal cell; CNS, central nervous system; CNT, concentrative nucleoside transporter; ENT, equilibrative nucleoside transporter; GLT-1, astrocytic glutamate transporter; HD, Huntington's disease; HMGB1, high mobility group box-1; IL, interleukin; IP3, inositol 1,4,5-triphosphate; KO mice, knockout mice; LPS, lipopolysaccharide; LTP, long-term potentiation; MDD, major depressive disorder; NLRP3, inflammasome; PD, Parkinson's disease; PKC, protein kinase C; Poly I:C, polyriboinosinic-polyribocytidylic acid; PSEN, presenilin; R, receptor; REM, rapid eye movement sleep; sAPP, soluble β-amyloid precursor protein; TLR4, toll-like receptor 4.

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function of the brain, which may be profoundly modified by purinergic signaling in neuron-glia networks. We will proceed according to the P1/P2Rs involved in these processes. The structure of this review will be the following: we will start with the basic, *quasi* physiological roles of these receptors and then continue with the pathophysiological ones, discussing at first the neurological and afterwards the psychiatric diseases which exhibit a dysregulation of purinergic receptors in their etiology. We searched in the PubMed database for publications on each purinergic receptor together with the attribute "behavior", and concentrated ourselves especially on the last 5–10 years. In addition, when an interesting review article has been found, we looked up some of the older publications referred in it.

This review will also discuss preferentially animal studies and therefore heavily rely on animal models of learning and memory tests, especially in rodents. A number of simple and regularly used test models are introduced to the newcomer in this field in Table 1.

2. P2 receptors in *quasi* normal behavior

2.1. P2X7 receptors in quasi normal behavior

P2XRs have been reported to be present in several CNS neurons mediating fast excitatory neurotransmission in response to the transmitter ATP (Nörenberg and Illes, 2000; Burnstock, 2015). This effect appears to be limited to certain neuronal pathways, e.g. in the medial habenula (Edwards et al., 1992), and nucleus locus coeruleus (Nieber et al., 1997), rather than broadly distributed over the brain, such as glutamatergic neurotransmission. In the forefront of our considerations among P2XRs are those of the P2X7-type, which are stimulated by large quantities of ATP released from damaged neurons and non-neuronal cells of the CNS. P2X7Rs, just as the other receptor-types of the P2XR-family, are built up of three identical or divergent subunits. Each subunit consists of two transmembrane regions, a large extracellular loop, and N- and C-terminal cytoplasmic ends (North, 2002; Torres et al., 1999). P2X7Rs have the following distinguishing characteristics: (1) They are stimulated – as mentioned above - only by high micromolar/millimolar concentrations of ATP, usually of non-neuronal origin (Surprenant et al., 1996). (2) Similar to other P2XRs, an initial contact with ATP leads to the conduction of a non-selective cationic current (Na^+, K^+, Ca^{2+}) through the receptor-channel, while long-lasting or repetitive contact with this agonist allows the passage of larger, usually positively charged, organic cations (Sperlágh and Illes, 2014; Harkat et al., 2017). (3) The C-terminus of P2X7Rs is much longer than that of other P2XRs and has been implicated in regulating receptor function, including signaling pathways, protein-protein interactions, and post-translational modification (Costa-Junior et al., 2011; Sluyter, 2017).

It is a matter of definition, whether fear and aversive behavior, in which the involvement of P2X7Rs has been unequivocally verified, can be termed as normal events; we prefer to define them as *quasi* normal behavior in distinction from more serious behavioral alterations observed during neurodegenerative illnesses. In fact, P2X7Rs are a major driver of neuroinflammation in the CNS and are preferentially localized at the resident macrophages of the brain and spinal cord, the microglial cells, although they exist, albeit at lower densities, also at astrocytes and oligodendrocytes, but probably not neurons (Illes et al., 2020; Kaczmarek-Hajek et al., 2018) (Fig. 1). Microglia are equipped with Toll-like receptors (e.g. TLR4) which detect lipopolysaccharide (LPS) derived from the cell membrane of gram-negative bacteria, during the respective infections (Young and Górecki, 2018). The ATP-sensitive P2X7R co-operates with TLR4 to release the inflammatory cytokine interleukin-1β (IL-1β; Illes et al., 2020). P2X7R stimulation promotes the assembly and activation of the inflammasome NLRP3, which via the caspase-1 pathway, proteolytically degrades pro-IL-1β to the mature IL-1β. Pro-IL-1β is synthesized in response to the binding of LPS to TLR4.

Microglia exists in a highly ramified form under resting conditions, but is transformed by harmful changes in brain homeostasis into an amoeboid form (Hanisch and Kettenmann, 2007). Amoeboid microglia on its behalf can phagocytose pathogenic bacteria or cell debris and release a number of bioactive molecules such as pro-inflammatory cytokines, chemokines, proteases, reactive oxygen/nitrogen species, and probably also the excitotoxic ATP and glutamate (Illes et al., 2020; Izquierdo et al., 2019).

In rodents, the hippocampus is a powerful circuit model which regulates memory formation and spatial navigation (Raskin et al., 2015). Contextual fear conditioning appears to depend on the hippocampus, basolateral amygdala and ventromedial prefrontal cortex (Illes et al., 2019b; Fiorenza et al., 2012). It has been reported that P2X7Rs participate in aversive memory processes; pharmacological blockade of this receptor with selective antagonists elicited dose-dependent impairments in memory acquisition, consolidation and retrieval in rats that were submitted to a contextual fear-conditioning task. The genetic deletion of P2X7Rs hampered the aversive memory processes of mice under these conditions (Campos et al., 2014).

In a hippocampal-dependent Y-maze task, IL-1β mRNA expression was induced in the hippocampus of wild-type but not P2X7R KO mice, suggesting that spatial memory performance was mediated by IL-1β (Labrousse et al., 2009). In perfect agreement with these results, IL-1R KO mice showed a slower rate of learning in the spatial memory paradigm of the Morris water maze test than their wild-type counterparts (Avital et al., 2003). Long-term potentiation (LTP), which is considered to be a cellular model of learning, was also absent in IL1-R KO mice, although it could be easily evoked in their wild-type controls. Air pollution by particles with a diameter of 2.5 μm or less are a major risk factor for global diseases and death. It was shown recently, that such particles cause neuroinflammation via the high mobility group box-1 (HMGB1)-NLRP3-P2X7R pathway in microglia, blocking hippocampal neuronal functions and in consequence cognitive impairment (Liu et al., 2022).

2.2. P2X4 receptors in normal behavior

The close proximity of *P2RX4* and *P2RX7* genes (both located in the long arms of chromosome 12 of humans and in chromosome 5 of mice)

Table 1
Simple learning and memory tests in rodents.

Novel object recognition (recognition memory). It is based on the tendency of rodents to spend more time exploring a novel object than a familiar one.
T-maze or Y-maze (exploratory/spatial memory). Differs in the shape of the maze and the starting position of the rodent. The animal has two arms to choose of (T) or three arms to choose of (Y). It is based on the tendency of the rodents to visit a new arm of the maze rather than a familiar arm, or alternatively to find a reward in one arm (usually food).
Morris water maze (spatial and long-term reference memory). It consists of a circular pool filled with water in which a transparent escape platform is located. The animals have to use the surrounding spatial cues to navigate towards the platform and escape from the water. When the animal learned in the training days to find the platform, on the testing day the location of the platform is changed.
Barnes maze (spatial learning and memory). In contrast to the T-maze or Morris water maze it does not require dietary restrictions or swimming to evaluate behavior. In a circular arena with 20 target zones in the periphery only one of the holes leads to the rodent's home cage. In the training days the animal learns to find the right target hole based on visual cues.
Passive avoidance (emotional learning and long-term memory). There are two compartments in the apparatus separated by a sliding door. The animals learn to associate the dark compartment with aversive experience, because they obtain here a mild electrical foot-shock. After the training phase, the time is measured after which the animals visit the dark compartment.
Contextual (Pavlovian) fear conditioning (associative context-driven learning). The animals learn to associate a neutral conditional stimulus (usually a neutral tone or environment) with an aversive unconditional stimulus (usually a mild electrical foot shock) and show a conditional response (usually a freezing behavior). After repeated pairing of the two types of stimuli, the animals start to fear both the tone and the training context. The time spent in freezing is measured under the different conditions.

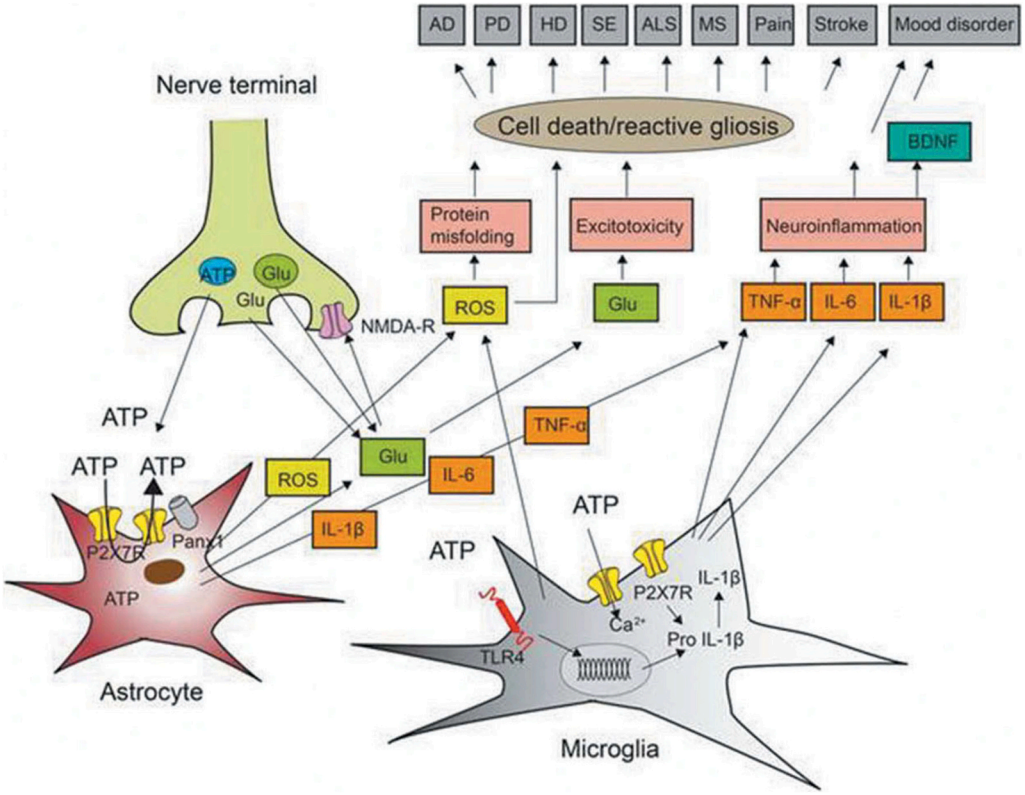

Fig. 1. Co-operation of neurons, astrocytes, and microglia to induce cell death/reactive gliosis during neurodegenerative and psychiatric illnesses. ATP and glutamate (Glu) are neurotransmitters released from nerve terminals but also gliotransmitters released/secreted from astrocytes and microglia. Hence, ATP may be released by Ca^{2+}-dependent exocytotic mechanisms from neurons/astrocytes, but also through P2X7 receptor-channels (P2X7Rs) or connexin hemichannels/pannexin-1 (Panx-1) channels from astrocytes. The P2X7Rs are entry pathways for extracellular Ca^{2+} (and also Na^{+}) into the cell interior. Stimulation of Toll-like receptors (TLR4Rs) by lipopolysaccharide (LPS) facilitates the production of pro-interleukin-1β in the cell nucleus. P2X7R activation leads to the caspase-1-dependent cleavage of pro-IL-1β to yield the mature IL-1β. Presynaptic N-methyl-D-aspartate (NMDA) receptors facilitate the release of glutamate. Reactive oxygen species (ROS) are secreted from microglial cells. ROS induces protein misfolding, glutamate is in high concentrations an excitotoxin, and the inflammatory cytokines IL-1β, IL-6 and tumor necrosis factor-α (TNF-α) cause neuroinflammation, accompanied by the release of brain-derived neurotrophic factor (BDNF). AD, Alzheimer's disease; PD, Parkinson's disease; HD, Huntington's disease; SE, status epilepticus; ALS, amyotrophic lateral sclerosis; MS, multiple sclerosis. From (Illes et al., 2019a) with permission.

suggests that P2X7Rs originate from *P2RX4* gene duplication (Di Virgilio et al., 2017). The overlapping expression of P2X4 and P2X7Rs has been documented in multiple tissues and non-excitatory cell types over the animal and human organism (Dubyak, 2007). Although the role of this co-expression has not been completely clarified, it is suggested that they play a role in inflammatory regulation (Burnstock, 2006). It has not yet been decided with absolute certainty whether two separate homomeric channels interact with each other or whether they constitute heteromeric P2X4/7 channels, although the former situation is more likely (Guo et al., 2007; Nicke, 2008; Antonio et al., 2011). While P2X7Rs probably do not occur in neurons, P2X4Rs have a wider distribution, being expressed both in neuronal and non-neuronal cells of the brain.

The antiparasitic drug ivermectin acts as a positive allosteric modulator of P2X4Rs, but does not interact with other P2XRs (Khakh et al., 1999). Ivermectin induced in wild-type mice a dose-dependent decrease in sensorimotor gating as assessed by pre-pulse inhibition of the acoustic startle reflex (Bortolato et al., 2013; Wyatt et al., 2014). By contrast, in $P2X4R^{-/-}$ mice ivermectin increased startle amplitude and failed to reduce the pre-pulse inhibition which enables neuronal systems of filtering out redundant or irrelevant stimuli from an overload of possible environmental stimuli reaching the brain. Later it was reported that stimulation of P2X4Rs can lead to dopamine hyperactivity and disruption of information processing which can be counteracted by the dopamine receptor 1 (D1R) agonist SKF 82958 (Khoja et al., 2019). Since deficits of pre-pulse inhibition have been reported in a wide spectrum of neuropsychiatric disorders that are characterized by cognitive deterioration, P2X4Rs might play a role in these illnesses.

In the healthy organism, P2X4Rs undergo rapid constitutive internalization and subsequent reinsertion into the plasma membrane (Bobanovic et al., 2002). The generation of a knock-in mouse in which the function of the non-canonical endocytosis motif in the C-terminus of the P2X4R subunit was inactivated, resulted in a missing constitutive endocytosis of the receptor (Bertin et al., 2021). In consequence, an increased number of P2X4Rs appeared at the surface of neurons accompanied with altered LTP and long-term depression (LTD) plasticity phenomena at CA1 synapses without affecting basal excitatory transmission. The increase in surface P2X4Rs translated into anxiolysis and deficits in spatial memory, as measured with the open-field and elevated plus maze sytems, respectively.

3. P2X receptors in neurodegenerative diseases

3.1. P2X7 receptors in Alzheimer's disease

In Alzheimer's disease (AD), the amyloid beta protein (Aβ) forms extracellular aggregates around neurons termed amyloid plaques, while the hyperphosphorylated tau protein is located intracellularly in form of neurofibrillary tangles. Both morphological changes have been considered to be hallmarks of AD (Picanco et al., 2018; Illes et al., 2019a; Francistiová et al., 2020), although increasing evidence indicates that there is moderate correlation between the presence of amyloid plaques/neurofibrillary tangles with the degree of cognitive decline, pathognomonic for AD (Reitz and Mayeux, 2014). In fact, plaques and tangles are not uncommon in the brains of non-demented, healthy old people (Denver and McClean, 2018; Malek-Ahmadi et al., 2016). In addition, hopes attached to the therapeutic potential of monoclonal anti-amyloid antibodies turned out to be unfounded, or in case of the recent lecanemab clinical study, of little use (Walsh et al., 2022). Lecanemab cleared successfully amyloid plaques in early AD, but had only small effect on cognitive decline. Thus, the favorable influence of another IL-1R blocking antibody on cognitive abilities measured in the Morris water maze and contextual fear conditioning tests determined in a triple

transgenic AD mice (Kitazawa et al., 2011) could not be extended to a wide population of human patients.

Nonetheless, most of the available animal models of this disease are either transgenic mice obtained by random integration of gene variants that encode proteins implicated in AD pathology (Götz et al., 2018) or rodents injected with Aβ into their brains (see below). Especially the mutations in either of three genes, namely β-amyloid precursor protein (APP), presenilin1 (PSEN1), or presenilin2 (PSEN2) account for most familial AD cases (Armstrong, 2013). However, in human patients, AD with autosomal dominant inheritance or early-onset AD with genetic risk are much less common than late-onset AD with polygenic causality, pointing out the somewhat limited applicability of the transgenic animal models for drawing clinically relevant conclusions.

In several transgenic mouse models of familial AD, the levels of P2X7R mRNA and P2X7R protein considerably surmounted those measured in wild-type animals (Parvathenani et al., 2003; Lee et al., 2011). Similar changes were observed in AD post-mortem brains, when compared with the non-demented controls (Martínez-Frailes et al., 2019). These results and the beneficial effect of the brain permeable P2X7R antagonist Brilliant Blue G (BBG; Jiang et al., 2000) on cognitive deficits in a mouse AD model (Chen, 2014) suggested the causal involvement of P2X7Rs in AD (Fig. 2). In the above experiments, the injection of soluble Aβ into the hippocampal CA1 region resulted in diminished spatial memory as demonstrated in the Morris water maze test. As a cellular model of memory, LTP in the hippocampal CA1 area was inhibited by soluble Aβ oligomers; this effect was prevented by the NR2B antagonistic ifenprodil (Li et al., 2011), suggesting that NMDA-Rs possibly located at dendritic spines mediate the depression of LTP (Lacor et al., 2007). Whereas CA1-LTP of the hippocampus induced by high frequency stimulation was inhibited by Aβ, granule cell-LTD induced by low frequency stimulation was increased by this peptide (Chen et al., 2013).

While P2X7R activation can induce inflammatory signaling pathways, particularly in microglia, the contribution of astrocytic P2X7Rs to synaptic changes and protein aggregate clearance in AD is also of eminent significance (Beltran-Lobo et al., 2022). Astrocytes are implicated in the deterioration of synaptic transmission in AD, affecting both excitatory glutamatergic and inhibitory GABAergic synapses (Andersen et al., 2022). Aβ induces calcium dysregulation in astrocytes which can alter their ability to modulate neurotransmission (Chow et al., 2010; Haughey and Mattson, 2003).

Despite evidence that supports a role for P2X7Rs in AD pathogenesis, there are also data which favor a neuroprotective role (Delarasse et al., 2011; Darmellah et al., 2012). It has been demonstrated that P2X7R stimulation activated the beneficial, non-amyloidogenic processing of APP. In this pathway, an α-secretase cleaves APP within the Aβ peptide sequence, which precludes the formation of neurotoxic Aβ peptides (generated by β-secretase) and produces soluble (s)APPα, a neurotrophic and neuroprotective fragment (Mattson, 1997). Behavioral analysis contradicts these results, since systemic administration of BBG decreased spatial memory impairment and cognitive deficits induced by intra-hippocampal injection of Aβ in an AD rat model (Chen, 2014).

However, Aβ peptides are not the only neuro-damaging and cognition disturbing factors in AD; in a number of AD mouse models, the genetic lack of P2X7Rs prevented microglial activation and the release of the two chemokines CCL3 (Martin et al., 2019) and CCL4 (Carvalho et al., 2021). The Aβ-mediated release of CCL3 is known to be associated with pathogenic $CD8^+$ T cell recruitment. Under both conditions, P2X7R deficiency improved neuroinflammation by reducing microglia activation as well as restored long-term synaptic plasticity and hippocampal-dependent spatial memory.

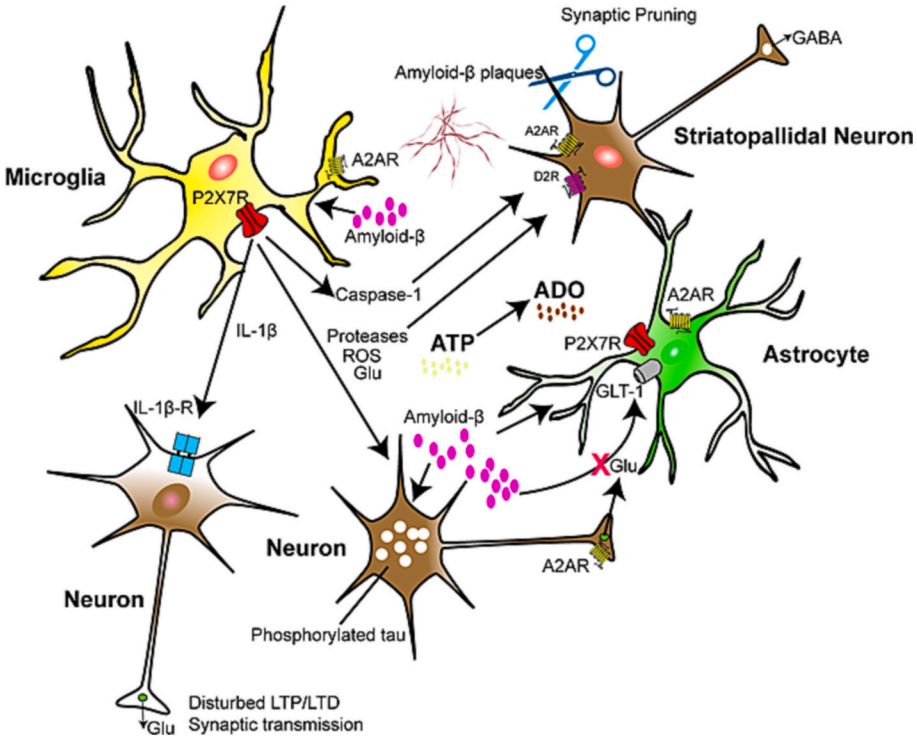

Fig. 2. ATP is released by exocytotic and non-exocytotic mechanisms from all neuronal and non-neuronal cells of the brain. Then, it is rapidly and enzymatically degraded to its active metabolite, adenosine. Soluble β-amyloid (Aβ) aggregates and thereby forms fibrillary plaques surrounded by microglial cells which phagocytose Aβ via P2Y4R activation. Aβ also directly damages neurons and increases the extracellular concentration of glutamate by inhibiting its astrocytic uptake through the GLT-1 transporter. Microglia are endowed with P2X7Rs, whose stimulation by high concentrations of ATP causes the activation of intracellular caspase-1, triggering thereby the apoptotic caspase cascade. P2X7R-mediated processes result in the release of inflammatory cytokines (e.g. IL-1β), proteases, reactive oxygen species (ROS) and the excitotoxic glutamate (Glu). During AD, hyperphosphorylated Tau forms intracellular neurofibrillary tangles in neurons. All these damaging conditions lead to neuronal necrosis and microglial apoptosis. The binding of IL-1β to its receptors at neurons modifies long-term potentiation (LTP) and -depression (LTD), as well as synaptic transmission. Microglial activation causes synaptic pruning during CNS development, but when becoming excessive, may foster in adults neurodegeneration. A2ARs are located at microglia, astrocytes and neurons. These receptors presynaptically facilitate the release of glutamate and also inhibit the uptake of glutamate into astrocytes. Postsynaptically, A2ARs are co-localized with D2 dopamine receptors at striatopallidal GABAergic output neurons and form heteromeric complexes mutually inhibiting their respective functions. This Fig. visualizes only the most important steps in the interaction of P2X7 and A2ARs with different cellular processes enhancing Aβ-induced regeneration in AD.

3.2. P2X7 receptors in Parkinson's disease

Hallmarks of pathological changes in Parkinson's disease (PD) are intra-neuronal and intra-axonal α-synuclein positive inclusions and loss of dopaminergic neurons in the substantia nigra pars compacta (Sorrentino and Giasson, 2020). Although the well-known motor disturbances (tremor, bradykinesia, muscular rigidity, impaired posture and balance) are the most prominent symptoms, patients suffering of PD often encounter mild cognitive decline and in the advanced state of this disease dementia (Aarsland et al., 2021). The P2X7R antagonist BBG has been shown to attenuate in the 6-hydroxydopamine model of hemiparkinsonism the short-term memory impairment demonstrated in the Morris water maze test, suggesting involvement of neurodegenerative P2X7Rs (Carmo et al., 2014a).

3.3. P2X7 receptors in Huntington's disease and other neurodegenerative disorders

Huntington's disease (HD) is a hereditary neurodegenerative disorder characterized primarily by motor dysfunction (hyperkinetic movement disorder termed chorea), due to expanded polyglutamine regions in the mutant huntingtin protein, leading to mitochondrial damage (Capiluppi et al., 2020). HD patients with extended polyglutamin regions-containing mutant huntingtin show already in the early phases of the disease cognitive decline (McColgan and Tabrizi, 2018), which may progress to dementia (Stahl and Feigin, 2020). Cortical and striatal neurons of transgenic mouse models of HD contain increased P2X7R mRNA and protein levels (Díaz-Hernández et al., 2009; Ollà et al., 2020). An interaction between P2X7 and P2Y2Rs appeared to contribute to the pathogenesis of HD, suggesting that the combination of P2X7R antagonists with P2Y2R antagonists might be a valid therapeutic option (Glaser et al., 2020; Glaser et al., 2021). Further, neurodegeneration associated with cognitive decline observed in animal models of such diseases (intermittent hypoxia (Deng et al., 2015) and sepsis-associated encephalopathy (Wang et al., 2022)) could be relieved by P2X7R antagonists.

3.4. P2X7 receptors in epilepsy and co-morbid neurodegenerative diseases

Usual co-morbidities of epilepsy are psychiatric disorders (depression, psychotic disturbances) and cognitive decline, progressing to dementia (LaFrance et al., 2008; Gil et al., 2022). P2X7R antagonism has been reported to suppress epileptic seizures (Beamer et al., 2017; Engel et al., 2021), but has also shown beneficial effects in neuro-psychiatric conditions commonly associated with epilepsy (Illes et al., 2019b; Francistiová et al., 2020).

4. P2Y receptors in normal behavior

4.1. P2Y1 receptors in normal behavior

P2Y1Rs are linked via a $G_{q,11}$ protein to inositol 1,4,5-triphosphate (IP3) and protein kinase C (PKC) to exert a range of effects especially in non-neuronal cells of the brain (Kügelgen and Wetter, 2000; Kügelgen, 2017; Jacobson et al., 2020). In this respect it is important to know that astrocytes are integrated into networks, in which individual astrocytes communicate with each other via gap junctions and probably also by P2YRs. Three connexins (Cx26, Cx30, Cx43) of which Cx43 is the most abundant, provide the molecular basis for gap junction channels that connect the cytoplasm of adjacent glial cells (Verkhratsky and Nedergaard, 2018; Theis and Giaume, 2012; Fujii et al., 2017). IP3 is a second messenger linked to G_q protein-coupled receptors such as P2Y1. IP3 diffuses freely through gap junctions, in the same way as Ca^{2+} itself does, and thereby supports the propagation of Ca^{2+} waves in astrocytic networks in conjunction with the release of ATP from one astrocyte that then stimulates P2Y1Rs on neighboring astrocytes (Pannasch and Rouach, 2013; Cheung et al., 2014). By using Ca^{2+} photometry, it has been shown that population astrocytic Ca^{2+} dynamics in the hippocampus were gated by sensory inputs (centered at the turning point of the T-maze equipment) and modified by the reward delivery during the encoding and retrieval phases (Lin et al., 2022). Hence, P2Y1Rs may participate via the regulation of astrocytic Ca^{2+} waves in the modulation of cognitive reactions.

Direct evidence for this assumption is also available. Bilateral microinfusion of the selective P2Y1R agonist MRS2365 into the rat medial prefrontal cortex (mPFC) attenuated pre-pulse inhibition of the acoustic startle reflex while having no impact on startle amplitude (Koch et al., 2015). In addition, stimulation of P2Y1Rs deteriorated performance accuracy in the delayed non-matching to position task in a delay-dependent manner and increased the rates of magazine entries consistent with both working memory disturbances and impaired impulse control. The delayed non-matching to position task is a widely used automated test of spatial memory. It has been concluded that activation of P2Y1Rs in the mPFC impairs inhibitory control and behavioral flexibility.

LTD was elicited in layer V pyramidal neurons of the rat mPFC by pairing low frequency stimulation with modest postsynaptic depolarization (Guzman et al., 2010). The activation of P2Y1Rs by ADP-β-S blocked LTD in a manner reversed by the specific P2Y1R antagonist MRS2179. ADP-β-S did not inhibit the LTD in preparations taken from $P2Y1R^{-/-}$ mice, but continued to act in those taken from $P2Y2R^{-/-}$ mice. All these results are in perfect accordance with the behavioral experiments reported for P2Y1R agonist infusion into the mPFC which showed deterioration of learning behavior.

4.2. P2Y2 receptors in normal behavior

P2Y2Rs are coupled to $G_{q/11}$, and their intracellular second messengers are IP3 and PKC. The stimulation of P2Y2Rs had assumedly opposite effects to those of P2Y1Rs by activating memory and cognitive functions (Alhowail et al., 2020); in these experiments P2Y2R KO mice were used in comparison with wild-type controls, but no P2Y2R agonists were studied in the wild-type animals. In the behavioral Y-maze test, there were spatial memory defects observed, in that significantly fewer entries into the novel arm were recorded in $P2Y2R^{-/-}$ mice, in contrast to measurements in the wild-type mice.

4.3. P2Y12 receptors in normal behavior

P2Y12Rs are coupled to $G_{i,o}$ and thereby inhibit adenylate cyclase (Jacobson et al., 2020; Kügelgen, 2017). Their most important therapeutic effect is the inhibition of thrombocyte aggregation and thereby the blockade of blood clotting. Various pre-drugs or drugs (clopidogrel, prasugrel, ticlopidin) are used instead of acetyl salicylic acid in the case of need for the long-time prevention of thrombosis and stroke. However, P2Y12Rs are also localized at neurons and microglia and their agonists/antagonists have neurologic/psychiatric effects when applied via routes evading the blood-brain barrier.

In studies relating to the measurement of P2Y12R activities, behavior was tested in the respective KO mice (Zheng et al., 2019; Lowery et al., 2021). In comparison with wild-type mice, their $P2Y12R^{-/-}$ counterparts exhibited increased anxiety-like behaviors in the open-field and elevated plus maze tests and displayed deficits in memory in the radial-arm and Morris water maze tests (Zheng et al., 2019). Moreover, loss of P2Y12Rs decreased the level of noradrenaline and the expression of noradrenergic α_2Rs in the cerebellum and hippocampus. The male P2Y12R KOs showed increased burying behavior, and both sexes exhibited increased digging behavior in the marble burying and digging test (anxiety-dependent reactions). In the novel object recognition test, the $P2Y12R^{-/-}$ mice had a higher recognition preference for a novel object than the wild-type mice, demonstrating enhanced associative learning, but no difference in spatial learning and memory (Lowery

et al., 2021). Hence, the genetic deletion of P2Y12Rs caused quite divergent effects in the two laboratories, worsening of learning in the first (Zheng et al., 2019) and improvement or no change of learning in the second laboratory (Lowery et al., 2021). The reason for this discrepancy is presently not clear.

5. P2Y receptors in neurodegenerative diseases

5.1. P2Y1 receptors in Alzheimer's disease and hypoxic stroke

Disturbances in cognitive functions were observed after middle cerebral artery occlusion (MCAO) as a model of hypoxic stroke (Chin et al., 2013; Carmo et al., 2014b). MCAO caused a decline in sensory-motor functions and cognition as measured by the contextual fear conditioning test in wild-type mouse (Carmo et al., 2014b). A selective P2Y1R antagonist, MRS 2500 prevented the cognitive decline. Similarly, both the non-selective P2Y1R antagonist PPADS and the highly selective antagonist MRS 2500 prevented the decrease in working and reference memory performance (Y-maze and object recognition tests) (Carmo et al., 2014b).

Using the APPS1 mouse model of AD, chronic intracerebroventricular infusion of the P2Y1R inhibitor MRS2179 normalized hippocampal astrocytic and neuronal network dysfunction, as measured by in vitro two-photon microscopy (Reichenbach et al., 2018). These dysfunctions manifested themselves as higher spontaneous calcium signal amplitudes and less pronounced LTP in the AD model mice, than in their respective controls. In addition, deficits in spatial preference learning and memory of APPS1 animals were also reversed by chronic P2Y1R inhibition.

5.2. P2Y2 receptors in Alzheimer's disease

P2Y2Rs have been found to be up-regulated in the brain of an AD model mouse within 10 weeks of age, and then decreased after 25 weeks of age, as compared to littermate controls expressing low levels of P2Y2Rs (Ajit et al., 2014). These findings were taken as an indication that the P2Y2R is important for the recruitment and activation of microglial cells in the AD brain and that they may regulate neuroprotective mechanisms through microglia-mediated clearance of Aβ (Ajit et al., 2014; Weisman et al., 2012). Accordingly, the levels of naturally occurring P2Y2R antibodies in the plasma of AD patients and cognitively normal study participants positively correlated with cognitive and functional performances (Jian et al., 2022). Thus, a decrease of humoral immunity against P2Y2Rs might occur in AD patients.

5.3. P2Y12 receptors in Alzheimer's disease

Microglia change their purinergic receptor expression during the activation procedure, which takes place in several steps (Szepesi et al., 2018; Illes et al., 2020). The somata of the resting/surveilling microglia remain at the same place for rather long periods of time, while the microglial processes are remarkably motile and continuously scan the parenchymal environment within non overlapping territories (Nimmerjahn et al., 2005; Kügelgen, 2017). Process-located microglial P2Y12Rs sense ATP, released from injured tissue into the extracellular space, and govern process extension. In the next step of activation, process retraction and P2Y12R downregulation occurs (Koizumi et al., 2013). Then, the phenotype of these cells becomes amoeboid and P2Y6 and P2Y4Rs appear to steer the phagocytotic (Abiega et al., 2016) and pinocytotic (Li et al., 2013) activities, respectively.

Microglia can phagocytize extracellular tau oligomers and monomers in AD via membrane-associated actin remodeling (Das and Chinnathambi, 2021). In response to tau oligomers, microglial P2Y12Rs colocalize with the remodeled membrane-associated actin network as a component of migration. Furthermore, P2Y12Rs mediated also internalization of the repeat domain of tau (tau^{RD}) into phagocytotic microglia, and degradation of accumulated tau^{RD} was executed by the lysosomal pathway (Chidambaram et al., 2022). A down-regulation of the *P2Y12R* gene in brains of AD patients and model mice bearing Aβ and tau pathologies were reported, and it was stated that this could be a sensitive index of neuroinflammatory responses to AD-related neurodegenerative processes (Maeda et al., 2021). It was soon afterwards confirmed that in AD patients, microglial phenotypes showing loss of P2Y12R, but consistent expression of the marker Iba1 were increasingly prevalent around Aβ plaques (Kenkhuis et al., 2022). Thus, microglia rather than neurons may participate in the behavioral responses reported above.

6. P2X receptors in psychiatric diseases

6.1. P2X7 receptors in major depression

Major depressive disorder (MDD) is a mental illness, with symptoms of extreme sadness, depressed mood, and loss of interest that persists for at least 2 weeks (Malhi and Mann, 2018). Environmental stressors and genetic factors in co-operation may initiate a plethora of morphologic and functional changes in the brain which eventually manifest themselves as depression (Jesulola et al., 2018). A battery of preferentially rodent tests has been routinely used to model this disorder, all based on the understanding that psychosocial stress is the most common and major risk factor of depression (Anderzhanova et al., 2017; Liu, 2017; Pryce and Fuchs, 2017). Chronic stress models (e.g. unpredictable chronic mild stress, unpredictable chronic stress, chronic social defeat stress, chronic immobilization stress) appear to be more impactful than the acute ones (e.g. tail suspension test, forced swim test, sucrose consumption, unavoidable foot shock) (Zhao et al., 2022). Of course, it has to be understood that depression-like behavior observed in such models is not identical with the MDD of patients.

More recently it was recognized that cognitive complaints are core symptoms of acute major depressive episodes and diminished ability to think or concentrate are critical for the diagnosis of MDD (Lam et al., 2014). MDD-induced cognitive deficits, occurring especially in the elderly, are defined as pseudodementia (Kiloh, 1961; Perini et al., 2019). In spite of its eminent significance for the psychosocial functioning of patients, experimental work dealing with cognitive disorders in MDD is scarce; e.g. it was just mentioned that anxiety and working memory deficits do occur in rodent models of MDD, and P2X7R-induced release of cytokines appears to be involved in the etiology of this disease (Furuyashiki, 2012). Similarly, injection of polyriboinosinic-polyribocytidylic acid (Poly I:C) to pregnant rats induced depression-like behavior and abnormal neurotransmission in adult, particularly female rat offsprings (Su et al., 2022). Open field, elevated plus maze, and forced swimming tests revealed that Poly I:C exposure led to increased anxiety-like and depression-like behaviors in female adolescent progenies. Brain region-specific elevation of the P2X7R- and NF-κB-NLRP3-IL-1β inflammatory signaling was observed in these rats modelled for depression-like behavior. Unfortunately, pharmacological antagonists of P2X7Rs or P2X7R KO mice intended to reverse or prevent Poly I:C-induced changes were not used in this series of experiments.

It has to be noted at this place that in 2018 Janssen Pharmaceuticals launched a randomized, placebo controlled, double blind, multicenter clinical trial of the blood-brain-barrier permeable P2X7R antagonist JNJ-54175446, which will be completed in 2024 (https://www.isrctn.com/ISRCTN44411633). In the meantime it was reported that JNJ-54175446 (500–600 mg) exhibited a dose-dependent plasma exposure without any serious adverse effects in study participants (Timmers et al., 2018). Another multiple ascending dose trial in a range of 40–450 mg showed that JNJ-54175446 was well tolerated by participants (Recourt et al., 2020).

6.2. P2X7 receptors in schizophrenia and mania/manic phase of bipolar disorder

Still less experimental attention has been devoted to cognitive disorders observed during the psychotic diseases, schizophrenia or the manic phase of bipolar disorder, and their treatment with P2X7R antagonists. Schizophrenia is characterized by distortions in thinking, perception, emotions, language, sense of self, and behavior (Zhang et al., 2022). Common experiences include hallucinations (hearing voices or seeing things that do not exist) and delusions (fixed, false beliefs). Mania is typically defined by increased psychomotor activity and elevated self-esteem (Zhang et al., 2022). Both in schizophrenia and mania, but also bipolar disorder, P2X7R-induced neuroinflammation is considered to be a major pathogenetic factor. A juvenile mouse model for schizophrenia was established by subchronic treatment with phencycline, an NMDA receptor antagonist, causing in humans hallucinations (Huang et al., 2021). These mice showed severe spatial learning and memory impairment in the Morris water maze and also schizophrenia-like symptoms (hypermotor behavior in the open-field). In fact, the phencyclidine-induced spatial memory disturbance and hypermotor behavior were reversed by blockade of P2X7Rs with JNJ47965567.

7. Adenosine receptors in normal behavior

7.1. A1 receptors in normal behavior

Of the four types of adenosine receptors, the A1- (negatively coupled to adenylate cyclase via $G_{i/o}$) and A2A-types (positively coupled to adenylate cyclase via G_s) have the highest binding affinity for adenosine (Fredholm et al., 2011; Burnstock et al., 2011; van Calker et al., 2019; Ferré et al., 2023). A1Rs are inhibitory both presynaptically on neurotransmitter (e.g. glutamate, dopamine, acetylcholine) release and postsynaptically on neuronal excitability, the latter one by increasing a potassium outward conductance.

A1R KO mice exhibited increased anxiety in the elevated plus maze (spending less time in the open, than in the closed arms) and the dark-light box (spending less time in the lit, than in the dark compartment); they were also more aggressive in the resident-intruder test than their wild-type controls (Johansson et al., 2001; Giménez-Llort et al., 2002). However, they showed similar memory acquisition patterns when assessed for spatial reference and working memory in the Morris water maze task (Giménez-Llort et al., 2005).

A1Rs are widely distributed in the CNS and are intimately involved in sleep regulation; in different animal models, extracellular adenosine concentrations vary according to the circadian rhythm and are especially high in brain regions involved in sleep control, such as the basal forebrain (Elmenhorst et al., 2017; Peng et al., 2020). The explanation for the relationship between extracellular adenosine and sleepiness is self-explanatory; the daytime activities consume the energy resources of the body and thereby enzymatic degradation produces adenosine which then causes sleepiness. Astrocytes contain both concentrative and equilibrative nucleoside transporters and therefore significantly contribute to setting the extracellular adenosine levels (Parkinson et al., 2011).

In the basal forebrain, extracellular adenosine activates A1Rs and facilitates the transition to sleep by reducing the action potential frequency of wakefulness-promoting neurons (Thakkar et al., 2003). Microdialysis perfusion of an antisense oligonucleotide against the mRNA of the A1R in the magnocellular cholinergic region of the basal forebrain of freely behaving rats, decreased the non-rapid eye movement sleep with an increase in wakefulness duration. A further argument supporting the role of A1Rs in the induction of sleep is that sleep-deprivation increases the extracellular levels of adenosine (Porkka-Heiskanen et al., 2000) and enhances A1R expression in the basal forebrain (Elmenhorst et al., 2017; Basheer et al., 2007).

7.2. A2A receptors in normal behavior

In contrast to A1Rs, A2ARs are excitatory, especially by increasing the intra-synaptic concentration of glutamate by promoting neuronal release and by inhibiting the astrocytic glutamate uptake transporter GLT-1, respectively (Fredholm et al., 2011; van Calker et al., 2019; Ferré et al., 2023). Postsynaptically, A2ARs are highly enriched in striatopallidal neurons, with lower presence in other parts of the brain, such as cortex and hippocampus. In the striatum, A2A/dopamine receptor 2 (D2) complexes are localized on the GABAergic, enkephalin-containing striato-pallidal output neurons, while the A1/dopamine receptor 1 (D1) complexes are located on the GABAergic substance P-containing striatonigral output neurons. It is important to mention that both classes of adenosine receptors are able to oligomerize also with a range of other transmitter receptors, the most important of which are the A2A/metabotropic glutamate receptor 5 (mGluR5), and A2A/D2/cannabinoid 1 (CB1) receptor complexes with different functional consequences. Thus, the striatal A2AR is uniquely positioned to integrate dopamine and glutamate signaling through multimeric A2AR/D2R and A2AR/mGluR5 heterocomplexes to modulate synaptic plasticity and control cognition in normal and disease conditions (Chen, 2014; Lopes et al., 2021; Merighi et al., 2022; Ribeiro et al., 2023).

The striatum (especially its dorsomedial part, and the nucleus accumbens) is a critical site for the control of cognitive behaviors. Indeed, activation of striatopallidal A2ARs exerts an inhibitory control on a variety of cognitive processes, ranging from working memory (Li et al., 2018), to goal-directed behavior (Li et al., 2015), motor sequence learning (He et al., 2022), strategy shifting (Zhou et al., 2019) and decision making (Sun et al., 2023). The use of opto-genetic A2ARs and focal A2AR KO strategies showed that these receptors in fact exert such a control, but do it at the expense of habit formation (Li et al., 2015). In addition, when conditional striatum-specific A2AR KO mice were tested for their reactions on latent inhibition and pre-pulse inhibition, it was found that neither learned inattention (as measured by latent inhibition), nor sensory gating (as indexed by pre-pulse inhibition) required the integrity of striatal A2ARs (Singer et al., 2013).

In spite of their relatively low density, hippocampal A2ARs also regulate cognitive functions in rodents (Li et al., 2015). A complete cognitive behavioral analysis was carried out in conjunction with the assessment of neurogenesis and sub-synaptic protein expression in A2AR constitutional KO mice (Moscoso-Castro et al., 2017). The authors found a broad cognitive impairment, including worsened performance in the Y-maze test (working memory), radial arm maze (spatial memory), passive avoidance test (emotional learning), and active avoidance (associative learning) in the A2AR KO mice when compared with their wild-type counterparts. It has been also observed that the genetic deletion of A2ARs decreased new-born hippocampal neuron proliferation and concomitant changes in synaptic protein expression. The integration of newborn granule cells to the hippocampal circuitry confers an extra degree of plasticity that is crucial for the acquisition of certain types of contextual memory (Deng et al., 2010; Sahay et al., 2011).

Recently, GABAergic A2AR-containing neurons localized in the lateral septum (LS) region of the brain have been found to induce depressive-like behavior in mice via projections sent to the dorsomedial hypothalamus (DMH) and lateral habenula (LHb) (Wang et al., 2023). The authors used a novel transgenic mouse line (A2AR-tag mice), A2AR-Cre mice, the injection of A2AR and/or a fluorescent dye expressing virus into the LS, and immunofluorescence microscopy for the identification of A2ARs in the LS-DMH and LS-LHb neuronal pairs. Hence, another group of extrastriatal GABAergic neurons were identified to be of significance to regulate depressive-like responses to acute and chronic stress.

A2ARs can be found in addition to neurons also on astrocytes, microglia and oligodendrocytes (Borea et al., 2018). All these non-neuronal cells may play a role in cognitive functions. Selective deletion of A2ARs in astrocytes results in GLT-1-mediated disruption of

glutamate homeostasis, characterized by increased presynaptic glutamate release, NMDA-R 2B subunit upregulation, and increased internalization of AMPA-Rs; consequently the psychomotor response to the NMDA-R antagonistic MK-801 (irreversible NMDA-R antagonist) increases and the efficiency of the working memory decreases (Matos et al., 2015). Female rats prenatally exposed to the glucocorticoid dexamethasone exhibited memory impairments at adulthood together with a disruption of neuronal synchronization between the mPFC and the dorsal hippocampus (Duarte et al., 2019). These functional deficits were paralleled by microglia hyper-ramification in the dorsal hippocampus and decreased ramification in the mPFC. The chronic blockade of A2ARs which are core regulators of microglia morphology and physiology, ameliorated the cognitive deficits.

Collectively, the ability of striatal A2ARs to function as a common "break" mechanism to constrain various cognitive functions suggest that pharmacological A2AR antagonism is pro-cognitive for selectively alleviating cognitive deficits in pathological conditions. This view has a high translational potential because of the recent approval of the A2AR antagonist istradefylline by the U.S. Food and Drug Administration to treat OFF-patients of Parkinson's disease (Chen and Cunha, 2020). Thus, A2AR antagonists may offer an opportunity for targeting the A2AR to improve cognitive dysfunction under various neuropsychiatric conditions.

8. Adenosine receptors in neurodegenerative diseases

8.1. A1 receptors in hypoxia, Alzheimer's disease, and Huntington's disease

A1R activation exerts broad neuroprotective effects against various CNS damaging conditions (Stone et al., 2009; Cunha, 2001). These effects are due to the A1R-mediated inhibition of voltage-dependent Ca^{2+} influx, the presynaptic blockade of glutamate release, and membrane hyperpolarization by the activation of an inwardly rectifying potassium current (Wardas, 2002; Gomes et al., 2011).

In hypoxia or ischemia, extracellular adenosine levels greatly increase due to elevated release and breakdown of ATP, and adenosine extrusion from compromised cells by the reverse operation of a concentrative nucleoside transporter (CNT) (Dale et al., 2000; Stockwell et al., 2017). This increased extracellular adenosine concentration proved to be protective via A1R activation against the effects of hypoxia/ischemia in the hippocampus (Stockwell et al., 2017). By contrast, in hippocampal slices of A1R KO mice the functional recovery from in vitro hypoxia - the incubation-medium was saturated with 95% N_2 + 5% CO_2 instead of the usual 95% O_2 + 5% CO_2 - was slower than in the respective slices prepared from wild-type mice (Johansson et al., 2001).

Chronic intermittent hypoxia exposures were used in mice to model obstructive sleep apnea-hypopnea syndrome (Zhang et al., 2020). This treatment led to an increase in the memory errors as determined in the 8-arm radial maze test. The hypoxia-treatment caused both morphological damage in the hippocampal CA1 region and apoptosis in the hippocampus, determined by TUNEL-staining, and finally interfered with LTP efficiency in hippocampal brain slice preparations. Intraperitoneal injection of the selective A1R agonist 2-chloro-N6-cyclopentyl adenosine (CCPA) attenuated, while injection of the selective A1R antagonist 8-cyclopentyl-1,3 dipropylxanthine (DPCPX) potentiated the behavioral limitations as well as the associated morphological damage.

When a rat HD model was generated by the intrastriatal injection of the mitochondrial toxin, 3-nitopropionic acid, subsequent intrastriatal injection of the selective A1R agonist N6-cyclohexyladenosine (CHA) attenuated the 3-nitopropionic acid-induced neuronal death, and accordingly improved cognitive (Morris water maze test) and motor deficits (rotarod test) (Rabie et al., 2023). Further, in an established transgenic mouse model of HD (R6/2 mouse), binding studies with the tritium labelled selective A1R agonist, [^{3}H]cyclopentyladenosine ([^{3}H]CPA) revealed that the density of A1Rs was reduced in the cortex and striatum in comparison with age-matched wild-type mice (Ferrante et al., 2014). CPA was more effective in depressing field potential amplitudes in corticostriatal slices from R6/2 mice than in those prepared from their wild-type littermates.

By contrast to these findings, in two AD mouse models, with mild tau pathologies, the selective A1R antagonist rolofylline administered via the i.v. route, reversed tau pathology and cognitive decline (Angglada-Huguet et al., 2023), whereas in a third mouse model, which had a high expression of tau with a very aggressive phenotype starting at about 3 months of age, rolofylline failed to reverse the pathology. Imaging with several PET tracers was used to explore the morphological changes; the burrowing test, the fear conditioning test, and the Morris water maze test were used for behavioral analysis. Thus, in this case the blockade, rather than the stimulation of A1Rs had a beneficial effect. The authors hypothesized that A1Rs might inhibit adenylate cyclase and decrease cAMP levels through $G_{i,o}$-coupling, and therefore rolofylline could produce increased levels of cAMP, activating protein kinase A, which in turn stimulates the ubiquitin-proteasome system, that plays a role in the clearance of unfolded proteins such as tau (Anglada-Huguet et al., 2023).

8.2. A2A receptors in Alzheimer's disease

A2ARs are abundantly expressed in astrocytes and thereby are supposed to participate in the etiology of AD (Lopes et al., 2021). Although it was reported that reactive astrocytes generated Aβ in lower quantity than neurons, astrocytes mostly produce N-truncated Aβ species, which are highly prone to aggregation and more toxic than the species produced by neurons (Oberstein et al., 2015). The increase in glutamate toxicity may be partly due to the Aβ-induced blockade of glutamate uptake into astrocytes (Matos et al., 2012). A small adenosine analogue (designated J4) that inhibited the equilibrative adenosine transporter ENT1, prevented the decline of spatial memory in an AD mouse model (Lee et al., 2018). In addition, chronic treatment with J4 normalized the impaired basal synaptic transmission and LTP at Schaffer collateral-CA1 synapses. J4 also counteracted the elevation of astrocytic A2ARs in the hippocampus and cortex of this AD model mouse.

Regular consumption of coffee, containing the mixed A1/A2AR antagonistic caffeine, has been shown to have a beneficial effect on cognitive decline in humans suffering of AD (Flaten et al., 2014). In perfect agreement with this finding, the i.c.v. administration of $A\beta_{25–35}$ to mice displayed impaired performance in both inhibitory avoidance (passive avoidance) and spontaneous alternation (alternation in the pursue of different tasks) tests (Dall'Igna et al., 2007). Subchronic treatment for 4 days with daily injections of either caffeine or the selective A2AR antagonist SCH58261 had no effect alone but prevented the Aβ-induced cognitive impairment in both tests.

Chronic treatment with caffeine in AD animal models improved memory and mitigated accumulation of amyloid peptides and hyperphosphorylated tau proteins (Arendash et al., 2006; Laurent et al., 2014). This was confirmed to be due to the blockade of A2ARs, since in an AD model mouse, the genetic deletion of this receptor-type protected from tau pathology-induced deficits of spatial memory and hippocampal LTD (Laurent et al., 2016). Oral therapy using a specific A2AR antagonist (MXS-3) improved memory and reduced tau hyperphosphorylation in THY-Tau22 mice. Further, in another mouse model of AD (APP/PS1), associative LTP was abolished in CA3 pyramidal cells of the hippocampus at an early stage of development (Da Viana Silva et al., 2016). This was caused by activation of A2ARs, because neutralization of these receptors by acute pharmacological inhibition or downregulation driven by shRNA interference restored associative CA3-LTP.

Altogether, it appears that increased expression of A2ARs in cognition-relevant areas of the brain was accompanied in AD patients with impaired memory retention and consolidation (Orr et al., 2015; Temido-Ferreira et al., 2020). Selective A2AR antagonism by pharmacological means or genetic deletion of these receptors in general,

counteracted memory impairment in diverse mouse models of AD (Canas et al., 2009; Da Viana Silva et al., 2016; Faivre et al., 2018; Temido-Ferreira et al., 2020).

8.3. A2A receptors in Parkinson's disease

When dopamine levels were decreased by reserpine to experimentally model PD in rodents, the pharmacological inactivation of A2ARs using non-selective (caffeine) or selective (ZM241385) antagonists has been reported to enhance short-term social memory (Prediger et al., 2005). These antagonists also improved, in spontaneously hypertensive rats (SHRs) and aged rats, the depressed short-term social memory and spatial learning (Takahashi et al., 2008; Uchida et al., 2014). Caffeine also reversed the memory disruption evoked by intra-nigral injection of the dopaminergic neurotoxin MPTP, in a two-way active avoidance task; in this test, rats learn to cross to the opposite side of a conditioning chamber to avoid a tone-signaled foot-shock (Gevaerd et al., 2001). Microinjection of 6-hydroxydopamine (with preceding injection of desipramine to protect noradrenergic neurons) was used to selectively damage pre-frontocortical dopaminergic neurons of rats (Kadowaki Horita et al., 2013). Afterwards decreased PFC dopamine levels and disturbed cognitive performance became evident, the latter measured by the object recognition and delayed alternation tasks; both were counteracted by the selective A2AR antagonist istradefylline. As already mentioned, istradefylline is an approved drug for the add-on treatment to levodopa in Parkinson's disease (PD) with "off" episodes (Brooks et al., 2012; Chen and Cunha, 2020; Brooks et al., 2012).

Another approach to develop a mouse PD model was to inject the neurodegenerative α-synuclein, a protein aggregate formed during human PD, into the striatum (He et al., 2022). When this neurotoxine was applied into the dorsolateral striatum, a selective impairment of sequence learning (by affecting sequence initiation), was observed. The selective A2AR antagonist istradefylline applied intra-peritoneally, improved sequence learning by preferentially supporting sequence initiation.

8.4. A2A receptors in Huntington's disease

A2ARs stimulate striatopallidal GABAergic neurons resulting in inhibitory actions, and, as already mentioned, form functional heteromeric complexes with D2-Rs inducing allostric inhibition (Glaser et al., 2020; Ferré et al., 2023). P2X7R activation also promotes glutamate release and neuronal damage. Thus, modulation of purinergic receptor stimulation, such as that mediated by A2A and P2X7Rs and subsequent aberrant Ca^{2+} signaling may contribute to neurodegeneration in HD.

Transgenic (Mazarakis et al., 2005; Brooks et al., 2012) and knock-in (Trueman et al., 2009) mouse lines of HD display impairments of reversal learning and working memory. Reversal learning measures the ability to actively suppress reward-related responding and to disengage from ongoing behavior, phenomena that are biologically and descriptively related to impulsivity and compulsivity in e.g. addiction (Izquierdo and Jentsch, 2012). Reversal learning disturbances are considered as symptoms of a fronto-parietal dysfunction. The effect of subacute treatment for 7 days with the selective A2AR antagonist SCH58261 on behavioral paradigms typical for a standard model of HD, the R6/2 transgenic mouse, has been also studied (Domenici et al., 2007). Such a treatment prevented alterations in emotional/anxious responses (plus maze, open field), but did not alter motor coordination in the rotarod test.

When two of the mouse lines used to model HD were cross-bred with an A2AR KO mouse, genetic inactivation of A2ARs prevented working memory deficits (8-arm radial maze) without modifying motor deficits (rotarod apparatus) (Li et al., 2015). Similarly, the A2AR antagonist istradefylline reverted working memory disturbances in one of the transgenic HD model mice and also LTD dysregulation at cortico-striatal synapses.

In an important review article, Patrizia Popoli and her co-authors concluded that A2ARs might mediate both beneficial (trophic and anti-inflammatory responses) and detrimental effects (stimulation of glutamate outflow and excessive glial activation) (Popoli et al., 2007). That implies that A2AR antagonists might cause either pro-toxic or neuroprotective effects depending on the different cell populations involved in the disease and also on the grade of disease progression. Thus, the outcome of a protracted therapy with these pharmaceuticals could certainly improve but in some cases also facilitate the degenerative process.

8.5. A2A receptors in obstructive sleep apnea-hypopnea syndrome, autism spectrum disorder, and fragile X syndrome

Obstructive sleep apnea-hypopnea syndrome (OSAHS) is widely known for the caused multiple systems damage, especially neurocognitive deficits in children (Koo and Nam, 2016). Chronic intermittent hypoxia was induced in a chamber to produce hypoxia-reoxygenation episodes in order to model OSAHS in mice (Li et al., 2022); this treatment evoked memory dysfunction manifested by increased error rates in the radial arm maze test. The stimulation of A2ARs by CGS21680 exacerbated memory impairment, while A2AR inhibition by SCH58261 or genetic deletion of the receptor exhibited the opposite effect. Similarly, blockade of A2ARs by long-time oral application of the mixed A1/A2AR antagonist caffeine, improved the behavioral deficits monitored by the Y-maze test in a mouse model of type-2 diabetes (Duarte et al., 2012). In fact, OSAHS is known to be associated with increased risk of type 2 diabetes (Martínez Cerón et al., 2015).

Autism spectrum disorder is characterized by severe core deficits in sociability and communication, as well as by repetitive behaviors and impairments in emotional functioning, leading to increased irritability, anxiety, and impulsivity (Lecavalier et al., 2006; Domenici et al., 2019). The BTBR inbred mouse strain shows robust behavioral phenotypes with analogies to the above diagnostic symptoms of autism. Acute, systemic treatment with the A2AR agonist CGS21680 attenuated elevated self-grooming and reversal learning deficit in the BTBR mouse model, whereas it did not affect self-grooming and probabilistic reversal learning in B6 control mice (Amodeo et al., 2018).

In fragile X syndrome, the most common form of inherited intellectual disability, individuals show characteristics common to autism, such as impairment of communication and social interaction (Jacquemont et al., 2014; Domenici et al., 2019; Ferrante et al., 2021). Chronic oral treatment with istradefylline to block A2ARs, corrected cognitive learning deficits measured in the novel object recognition test in Fmrf1 KO mice (Ferrante et al., 2021). This was suggested to be due to the normalization of the exacerbated signaling through the metabotropic glutamate receptor 5 (mGlu5R) in the hippocampus.

9. Adenosine receptors in psychiatric diseases

9.1. A2A receptors in schizophrenia

Two hypotheses, those of dopaminergic hyperfunction, and glutamatergic hypofunction, are widely accepted conceptual frameworks for understanding the pathophysiology of schizophrenia (Coyle and Tsai, 2004; Seeman, 2006). More recently, an emerging theory of schizophrenia postulates that hypofunction of adenosine signaling may contribute to its pathophysiology (Boison et al., 2012). Augmentation of adenosine effects by pharmacological inhibition of adenosine kinase, the key enzyme for adenosine clearance, exerted antipsychotic-like activity. Further, overexpression of adenosine kinase in transgenic mice was associated with attentional impairments linked to schizophrenia-like reactions (Yee et al., 2007; Boison et al., 2012; Moody et al., 2020).

A2AR agonists have been reported to cause behavioral effects similar to those of dopaminergic antagonists, which are approved drugs to treat positive symptoms of schizophrenia (Rimondini et al., 1997; Domenici

et al., 2019). In fact, hyperlocomotion induced by D-amphetamine was reduced in A2AR KO mice when compared to the wild-type littermates (Moscoso-Castro et al., 2016). Moreover, these animals showed deficits in latent and pre-pulse inhibition, as well as in social interaction, and in the object recognition task.

Gfa2-A2AR KO mice exhibit astrocyte-specific genetic deletion of A2ARs. These mice showed an enhanced MK-801-induced psychomotor response and decreased working memory; this was accompanied by aberrant GLT-1 activity and increased endocytosis of AMPA-Rs (Matos et al., 2015). Accordingly, selective GLT-1 inhibition or blockade of GluR1/2 endocytosis prevented the psychomotor and cognitive phenotypes of Gfa2-A2AR KO mice.

9.2. A2A receptors in obsessive compulsive behavior and attention deficit hyperactivity disorder

Adenosine A2AR antagonists were efficient also in interacting with repeated quinpirole-induced behavioral alterations (Asaoka et al., 2019). Qinpirol is a selective dopamine D2 and D3R agonist which increases in mice locomotion and symptoms pathognomic for obsessive compulsive behavior (Szechtman et al., 1998). The A2AR antagonist istradefylline rescued abnormal excitatory synaptic function in medium spiny striato-pallidal output neurons of sensitized mice, and alleviated the quinpirole-induced abnormal behaviors (Asaoka et al., 2019). Hyperactivity of striato-pallidal neurons was electrophysiologically determined by recording spontaneous postsynaptic inhibitory current frequency; cognitive changes were determined by reversal learning in the T maze paradigm.

SHRs are frequently used as models of attention deficit hyperactivity disorder. When female Wistar and SHR rats were treated with caffeine for 14 days during the pre-pubertal period, and they were tested later in adulthood in the object recognition task, SHR, in contrast to Wistar rats, were not able to discriminate pairs of objects with subtle structural differences (Pires et al., 2010). In a subsequent study, it was found that caffeine administration from childhood in SHR, rescued recognition memory impairment (novel object recognition) in both sexes, but spatial memory disturbance (modified Y-maze test) was recovered only in female SHR rats (Nunes et al., 2018).

9.3. A2A receptors in agitated depression

Epidemiological data indicate that consumption of caffeine, the non-selective adenosine receptor antagonist, can reduce the risk of developing a depressive symptomatology (Lucas et al., 2011). A model of agitated depression was generated by bilateral olfactory bulbectomy of mice (Machado et al., 2020). Chronic caffeine treatment for 7 weeks prevented the hyperactivity (open-field test) and recognition memory impairment (novel object recognition, Y-maze) as well as rescued self-care (splash-test initiating grooming behavior). At the same time caffeine also prevented the pathological astrogliosis in the dentate gyrus of the hippocampus and neurodegeneration in the striatum and piriform cortices.

10. Conclusions

Purinergic receptors of the ATP/ADP, UTP/UDP- (P2X, P2YRs) and adenosine-sensitive (A1, A2AR) classes broadly interfere with cognitive processes both under normal and disease conditions. Of the P2XRs especially the P2X7R is intimately involved in learning processes during neurodegenerative diseases amplified by the release of high concentrations of ATP from neuronal and non-neuronal cells of the brain. Such neurodenerative disorders are AD, PD and HD, which all share the aggregation of intra- or extracellular protein deposits (amyloid β-protein and hyperphosphorylated tau [AD], α-synuclein [PD], and extended polyglutamin regions of mutated huntingtin [HD]), releasing high concentrations of ATP into the extracellular space. The subsequent activation of P2X7Rs causes neuroinflammation in response to the production of the inflammatory cytokine interleukin-1β, due to the co-activation of Toll-like receptors, by e.g. lipopolysaccharide, a constituent of the cell wall of gram negative bacteria. Further, P2X7Rs release a number of bioactive and cell damaging molecules such as additional pro-inflammatory cytokines, chemokines, proteases, reactive oxygen/nitrogen species, and probably also the excitotoxic ATP and glutamate. All these cell products are supposed to kill e.g. invading bacteria, but due to their non-specific effects also injure the brain parenchyma. Cognitive abilities belong to the highest order functions of the brain and as expected, neurodegenerative processes impair them and result in primary (AD) or secondary (PD, HD) dementia.

Chronic stress in conjunction with genetic predisposition are considered as most important etiological factors of major depression and bipolar disorder. Cognitive complaints are core symptoms of acute depressive episodes in MDD; they occur especially in the elderly and may proceed to pseudodementia. Anxiety and working memory deficits are placed in the forefront of the disease, and the P2X7R-induced release of cytokines appears to be causally involved in their development. Consequently, both P2X7R antagonists and IL-1R antagonists alleviate symptoms of neurodegenerative diseases, including the cognitive and anxiogenic ones. Similarly, in animal models of schizophrenia and mania, induced by phencyclidine or amphetamine application, P2X7R antagonists inhibit the hypermotor behavior and the spatial memory deficits.

P2YRs are coupled to G proteins, those of the P2Y1R type to $G_{q,11}$, which promotes the production and activation of IP3 and PKC, respectively. P2Y1Rs at astrocytes regulate Ca^{2+} wave propagation in astrocytic networks and thereby the fine-tuned modulation of cognitive reactions. Prefrontal P2Y1Rs disturb working memory and impulse control, while their antagonists have the opposite effect. In contrast to P2Y1Rs, P2Y12Rs appear to improve spatial memory and reduce anxiety-dependent behaviors, and the genetic deletion of this receptor has an opposite effect. P2Y12Rs have a preferential location at resting/surveilling microglial processes, which are highly mobile and by establishing contacts with numerous synapses in the brain are able to modulate neuronal functions.

ATP released in the brain is enzymatically degraded to adenosine; adenosine receptors are negatively (A1, A3) or positively (A2A, A2B) linked to the enzyme adenylate cyclase via G proteins. A1Rs mediate the inhibitory effects of accumulating adenosine on wakefulness-enhancing neurons due to degradation of the energy supplying ATP during daytime activities to its metabolite adenosine. A2ARs have been found to be preferentially localized in the striatum and nucleus accumbens, but at lower densities they occur also in other parts of the brain such as the hippocampus, frontal cortex, and lateral septum. They interact postsynaptically in an inhibitory manner with dopamine and cannabinoid receptors based on the construction of heteromeric A2A/D2 and A2A/D2/CB1-R complexes.

A2ARs are also intimately involved in the neurodegenerative diseases AD, PD, and HD; this is partly due to the activity of A2AR bearing astrocytes and microglia. In both cases, A2ARs have deleterious effects on neurons, by the amplification of neurodegeneration caused by the primary pathogenetic factors of these diseases (see above). Aβ and A2ARs increase the extracellular concentration of glutamate, the latter one by increasing transmitter release and by blocking glutamate uptake into astrocytes via the transporter GLT-1. Once more both Aβ, α-synuclein, and mutated huntingtin may induce aberrant Ca^{2+} signaling, just as A2ARs do due to their stimulation of the G_s-adenylate cyclase second messenger pathways. Therefore, according to expectations, in various animal models of AD and HD, the non-selective antagonist caffeine and the selective antagonist istradefylline both relieved cognitive disorders. Interestingly, A2AR antagonists had a favorable effect in animal models of schizophrenia, by mitigating the positive symptoms of this disease, and similarly, alleviated the disease burden in mania, the manic phase of bipolar disorder, obsessive compulsive behavior and attention-deficit

hyperactivity disorder.

Hence, extracellular ATP/ADP, UTP/UDP, and adenosine, after activation of their membrane receptors, may cause harmful effects especially by adding up to the neuronal damage brought about by neurodegenerative and psychiatric illnesses. The use of the respective receptor antagonists appears to alleviate these symptoms in animal disease models, and may be therefore important therapeutic targets for the development of future drugs.

CRediT authorship contribution statement

Peter Illes: Conceptualization, Writing – original draft. **Henning Ulrich:** Writing – review & editing. **Jiang-Fan Chen:** Writing – review & editing. **Yong Tang:** Writing – original draft.

Declaration of Competing Interest

All authors declare that they have no competing interest.

Data availability

The data can be found in the articles reported on.

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