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Review article

Purinergic modulation of glutamate transmission: An expanding role in stress-linked neuropathology

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ABSTRACT

Chronic stress has been extensively linked to disturbances in glutamatergic signalling. Emerging from this field of research is a considerable number of studies identifying the ability of purines at the pre-, post-, and peri-synaptic levels to tune glutamatergic neurotransmission. While the evidence describing purinergic control of glutamate has continued to grow, there has been relatively little attention given to how chronic stress modulates purinergic functions. The available research on this topic has demonstrated that chronic stress can not only disturb purinergic receptors involved in the regulation of glutamate neurotransmission, but also perturb glial-dependent purinergic signalling. This review will provide a detailed examining of the complex literature relating to glutamatergic-purinergic interactions with a focus on both neuronal and glial contributions. Once these detailed interactions have been described and contextualised, we will integrate recent findings from the field of stress research.

1. Introduction

Chronic stress is recognised to be one of the most common of all aversive modifiers of mammalian behaviour. The relationship between chronic stress a risk factor in the emergence and exacerbation of mood disturbance, including depression, is now very well established (Siegrist, 2008). As a result of this relationship a large body of work emerged that has focused on investigating exactly how stress modifies brain circuitry. Thus far, at a systems level, exposure to chronic stress has been demonstrated to induce a relatively consistent set of neurological alterations, including dendritic retraction (Christian et al., 2011), extensive synaptic loss (Krugers et al., 2010) and impaired neurogenesis (Morais et al., 2014), particularly within nuclei involved in cognition and emotional processing. While these changes are well established, the molecular level changes upon which they are based remain an area of intense research activity.

The ability of stress to modulate multiple neurotransmitter systems has been well described. Clinically, however, interventions directed towards modulating serotonin and norepinephrine release have proven to be of only modest efficacy (Walker, 2013). This situation has led to renewed interested in the potential role of the neurotransmitter L-Glutamate (Glu). Exposure to chronically stressful situations has been shown to potently disrupt glutamatergic signalling and recent studies investigating pharmacological manipulation of glutamatergic signalling have noted surprising levels of antidepressant activity (Featherstone et al., 2012; Maeng et al., 2008; Rasmussen et al., 2013). These observations have begun to motivate many working with the field to take a closer look at the critical systems in modulating glutamatergic tone. Of these, perhaps the most important appears to be the purinergic system.

Purines are a large family of compounds released alongside glutamate, and capable of extensively modulating glutamate via a plethora of receptors. The aim of the current manuscript is to compile existing knowledge of the role of purines in the modulation of glutamate neurotransmission in the healthy and chronically stressed brain. We will place a particular emphasis on the ability of astrocytes and microglia to bind and release purines to direct complex signalling processes and as potent neuro- and glio-modulators.

2. Purines: an overview

The term ‘purines’ refers to the family of compounds comprised of variably phosphorylated adenine nucleotides, principally being adenosine (Ado), adenosine monophosphate (AMP); -diphosphate (ADP);

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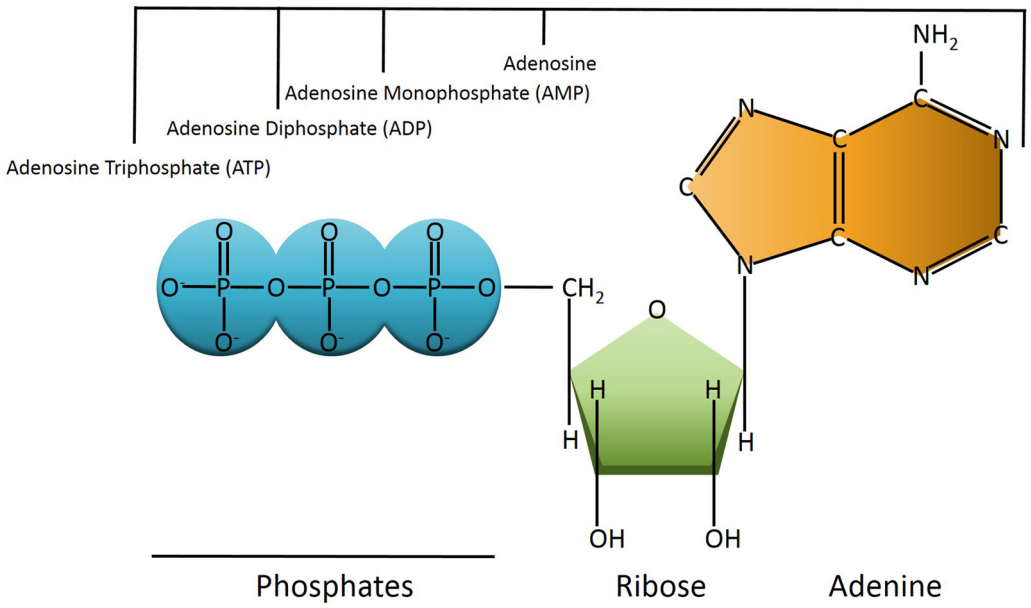

Fig. 1. Purinergic compounds. Each member of the purine family consists of an adenine and ribose backbone, either as is (adenosine), or with an additional one (AMP) to three (ATP) phosphate groups (Ralevic and Burnstock, 1998).

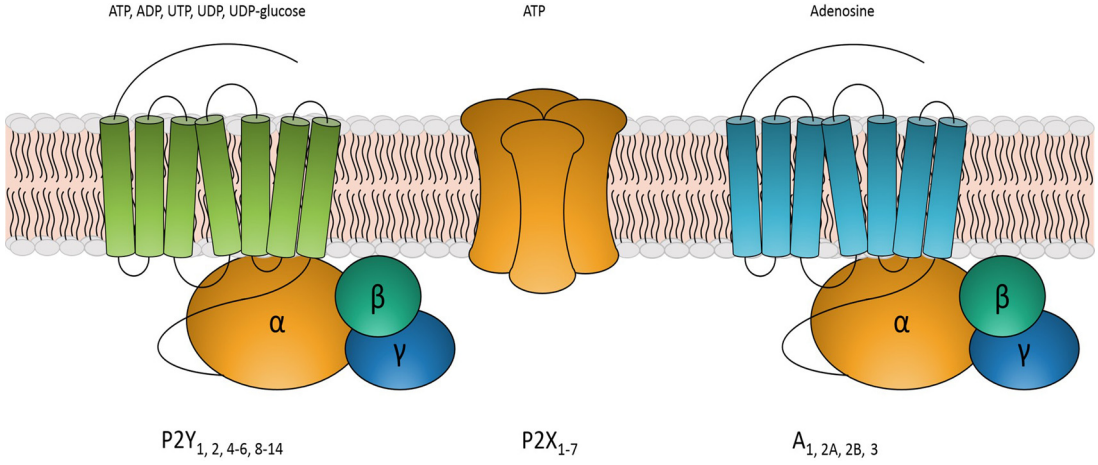

Fig. 2. Purinoceptors. The P2Y receptors are seven transmembrane GPCRs, which are sensitive to ATP as well as a number of purine derivatives, including ADP, UTP (uridine triphosphate), UDP (uridine diphosphate), and UDP-glucose. The ionotropic P2X receptors are arranged as homo- or heterodimers and exclusively bind ATP. When activated P2X receptors allow the transport of cations including Na^+, K^+ and Ca^{2+} across the plasma membrane. The four P1 receptors are metabotropic G-protein coupled receptors (GPCRs) sensitive to adenosine.

and -triphosphate (ATP)(see also Fig. 1). Purines are ubiquitously expressed in the central and peripheral nervous systems, and possess a multitude of trophic and neuromodulatory functions (Su, 1983; Rathbone et al., 1999; Ralevic and Burnstock, 1998). These endogenous nucleotides achieve their diverse range of biological functions in part due to the large family of plasma membrane receptors that bind these nucleotides. P1 receptors being activated by adenosine and the P2 receptors, which bind ATP and its various analogues (see Fig. 2) (Ralevic and Burnstock, 1998). P2 receptors can be separated into ionotropic P2X receptors, and metabotropic P2Y receptors. The P2X receptors are ligand-gated cationic channels, permeable to Na^+, K^+ and Ca^{2+}, and are arranged as homo- or heteromeric receptors comprised from seven cloned subunits ($P2X_{1-7}$). The P2Y receptors are seven-transmembrane-domain metabotropic G-protein coupled receptors (GPCRs) for which 12 subtypes have been identified ($P2Y_{1,\ 2,\ 4\text{-}6,\ 8\text{-}14}$)(Ralevic and Burnstock, 1998). Activation of P2Y receptors regulates K^+ channels, potentiates high-voltage-activated Ca^{2+} channels and triggers inositol 1,4,5-triphosphate (IP_3)-mediated release of Ca^{2+} from endoplasmic reticulum stores. In addition to binding ATP, P2Y receptors, can also be activated by ADP, uridine triphosphate and diphosphate (UTP and UDP), and uridine diphosphate-glucose (UDP-glucose)(Ralevic and Burnstock, 1998). Similar to P2Y receptors, all four cloned P1 receptors (A_1, A_{2A}, A_{2B}, and A_3) are seven-transmembrane-domain metabotropic G-protein coupled receptors in nature (for review see Ralevic and Burnstock, 1998).

Although the contribution of this family of compounds to intracellular energy metabolism and the electron transport chain within mitochondria has been recognised for half a century, the ability of purines to elicit synaptic currents and to induce and modulate the release of neurotransmitters has been progressively identified in only the last two decades.

3. Purinergic synaptic modulation

Both ATP and adenosine can act on their respective receptors to induce synaptic currents in neurons; however the manner in which