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Research Report

Purinergic P2X receptors presynaptically increase glutamatergic synaptic transmission in dorsolateral periaqueductal gray

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ABSTRACT

Purinergic P2X receptors have been reported to be present in regions of the midbrain periaqueductal gray (PAG). The purpose of this study was to determine the role of presynaptic P2X receptors in modulating excitatory and inhibitory synaptic inputs to the dorsolateral PAG (dl-PAG), which has abundant neuronal connections. First, whole cell voltage-clamp recording was performed to obtain excitatory and inhibitory postsynaptic currents (EPSCs and IPSCs) of the dl-PAG neurons. Our data show that α, β-methylene ATP (a P2X receptor agonist), in the concentration of 50 μM, significantly increased the frequency of miniature EPSCs without altering the amplitude of miniature EPSCs in eight tested neurons. The effects were attenuated by PPADS, an antagonist to P2X receptors. Furthermore, α, β-methylene ATP increased the amplitude of evoked EPSCs, and decreased the paired-pulse ratio of eEPSCs in ten neurons. In contrast, activation of P2X had no distinct effect on IPSCs. In addition, immunofluorescent methods demonstrate that P2X labeling was co-localized with a presynaptic marker, synaptophysin, in the dl-PAG. The results of the current study provide the first evidence indicating that P2X receptors facilitate glutamatergic synaptic transmission in the dl-PAG via presynaptic mechanisms.

1. Introduction

Adenosine triphosphate (ATP) is released from nerve terminals in the peripheral nervous system and in numerous regions of the CNS (Cunha et al., 1996; Salgado et al., 1996; Sawynok et al., 1993). ATP has been reported to be a mediator involved in synaptic transmission and integration within glial systems in the CNS (Cotrina et al., 2000; Edwards et al., 1992; Khakh, 2001; Stout et al., 2002). A family of ionotropic P2X purinoreceptors including seven P2X subtypes appears in the brain (Norenberg and Illes, 2000), and mediates the action of ATP as a fast neurotransmitter (Burnstock, 2000; Dunn et al., 2001; North, 2002).

Previous studies suggest that P2X receptors modulate glutamatergic and GABAergic synaptic transmission in the CNS, namely spinal cord, the nucleus tractus solitarius, medial habenula, locus coeruleus, hippocampus, and somatosensory cortex (Bardoni et al., 1997; Evans et al., 1992; Gu and MacDermott, 1997; Hugel and Schlichter, 2000; Jin et al., 2004; Mori et al., 2001; Nakatsuka and Gu, 2001; Nieber et al., 1997; Pankratov et al., 1998). For example, activation of P2X receptors has been shown to presynaptically alter the release

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of glutamate, GABA, glycine and vasopressin (Jin et al., 2004; Khakh and Henderson, 2000; Nakatsuka and Gu, 2001; Rhee et al., 2000; Troadec et al., 1998). Presynaptic modulation of transmitter release has been thought an important component of P2X receptor function in the brain.

The midbrain periaqueductal gray (PAG) receives abundant neuronal inputs from the dorsal horn of the spinal cord, hypothalamus as well as forebrain (Craig, 1995; Keay et al., 1997; Wiberg and Blomqvist, 1984). Also, the PAG sends descending neuronal projections to the medulla (Hudson and Lumb, 1996; Odeh and Antal, 2001) in regulating pain and autonomic activity (McGaraughty et al., 2003; Tjen-A-Looi et al., 2006; Verberne and Guyenet, 1992). Among regions of the PAG, the dorsolateral region (dl-PAG) contributes to an increase in arterial blood pressure and antinociception (Bandler et al., 1991; Behbehani, 1995).

Purinergic P2X receptors have been reported to appear in the PAG (Worthington et al., 1999). Activation of P2X receptors

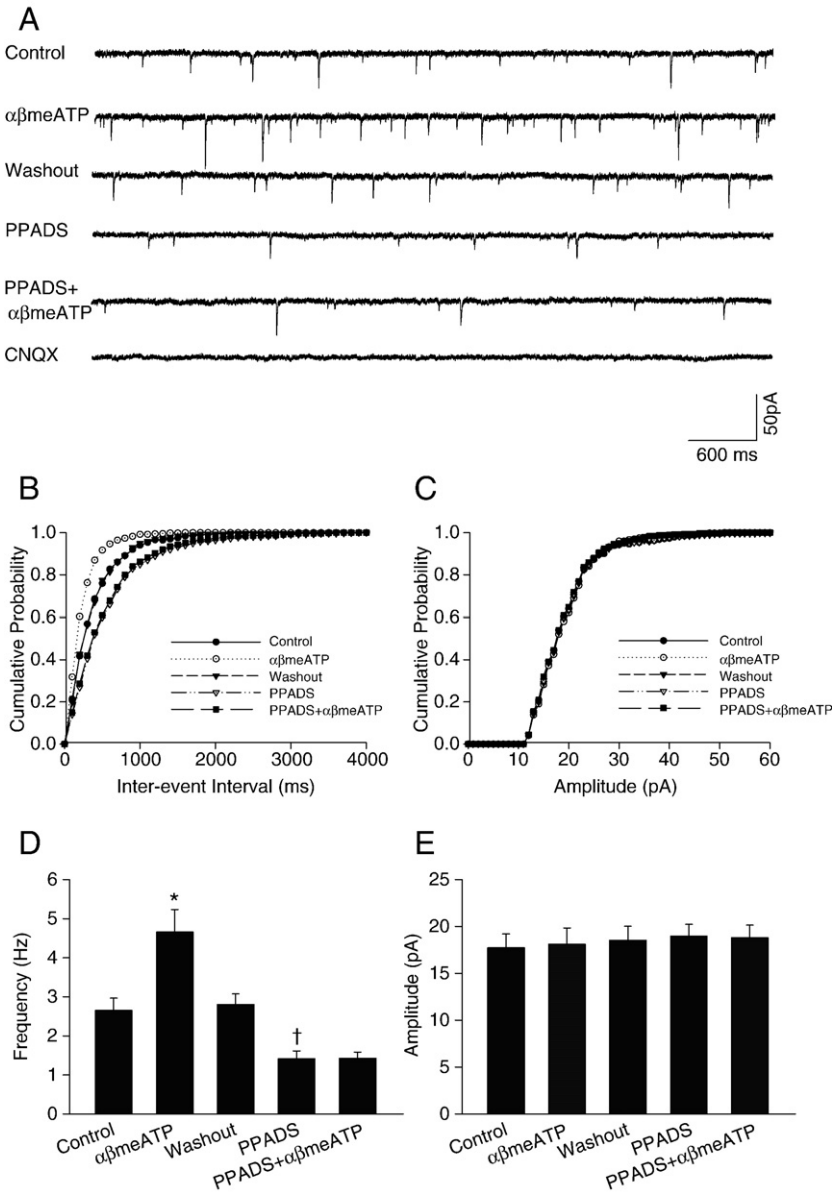

Fig. 1 – Effect of P2X receptors on the frequency of glutamatergic mEPSCs of the dl-PAG neurons. This experiment was examined in eight neurons tested. A: Representative tracings from a dl-PAG neuron show that 50 μM of α, β-me ATP elevated, but 20 μM of PPADS decreased the frequency of mEPSCs. The effects of α, β-me ATP were eliminated by PPADS. The mEPSCs recovered during washout and were completely abolished in the presence of 20 μM of CNQX. B and C: The cumulative probability analysis shows that α, β-me ATP decreased, but PPADS increased the inter-event interval of mEPSCs but did not alter the distribution pattern of the amplitude of the mEPSCs. D and E: Average data show the effects of P2X on the frequency and amplitude of mEPSCs in eight dl-PAG neurons tested. *$P<0.05$, α, β-me ATP vs. control and washout. †$P<0.05$, PPADS vs. control and washout. There was no difference in the frequency of mEPSCs between PPADS and PPADS plus α, β-me ATP.