1521-0103/389/S3/supplement: ASPET 2024 Annual Meeting Abstract
The Journal of Pharmacology and Experimental Therapeutics
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dx.doi.org/10.1124/jpet.470.876150
J Pharmacol Exp Ther 389: June 2024

The Journal of PHARMACOLOGY And Experimental Therapeutics

Central PI3K/MAPKs Pathway Provokes the Adenosine A3 Receptor Counteraction of Cholinergic Defenses Against Cardiovascular Aberrations in Septic Rats

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Abstract ID 87615 **Poster Board 470**

Despite the established role of systemic adenosine receptors in sepsis pathophysiology, little or no information is available on whether this action is shared by central adenosine receptors. Here, we tested the hypothesis that central adenosine A_3 receptors (A_3AR) moderate cardiovascular and neuroinflammatory sequels of sepsis and its neutralization by the cholinergic antiinflammatory pathway in rats. Sepsis was induced by cecal ligation and puncture (CLP) in rats instrumented with femoral and intracisternal (i.c.) catheters for hemodynamic monitoring and central drug administration, respectively. The CLP-evoked hypotension, reductions in time and spectral indices of heart rate variability (HRV) and shifts in cardiac autonomic balance towards parasympathetic dominance were mostly abolished following cholinergic activation (i.v. nicotine, 100 μg/kg) or A3AR blockade (i.c. VUF5574, 2 μg/rat). Moreover, central A3AR activation by 3-iodobenzyl-5'-N-methylcarboxamidoadenosine (i.c. IB-MECA, 4 μg/rat) intensified the hypotension and cardiac autonomic neuropathy induced by CLP and nullified the nicotine counteraction of septic manifestations. Immunohistochemical studies revealed that IB-MECA reversed the nicotine suppression of the upregulated protein expression of inflammatory (NFκB) and oxidative (NOX2) signals in neuronal pools of brainstem rostral ventrolateral medulla (RVLM) of septic rats. Such detrimental actions of IB-MECA on nicotine responses disappeared after i.c. administration of PD98059 (MAPK-ERK inhibitor), SP600125 (MAPK-JNK inhibitor) or wortmannin (PI3K inhibitor). Further, central inhibition of TNF α by infliximab eliminated the IB-MECA-induced rises in RVLM-NFκB expression and falls in HRV, but not blood pressure. The data implicates central PI3K/MAPK cascade in the A3AR suppression of the cholinergic protection against neuroinflammatory and cardiovascular insults of sepsis.

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