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ATP-independent activation of natriuretic peptide receptors

Laura K Antos, Sarah E Abbey-Hosch, Darcy R Flora and Lincoln R Potter*

Address: Department of Biochemistry, Molecular Biology and Biophysics, University of Minnesota, USA

Email: Lincoln R Potter* - potter@umn.edu

* Corresponding author

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Natriuretic peptide receptor A (NPR-A) is an essential cardiovascular regulator that is stimulated by atrial natriuretic peptide and brain natriuretic peptide, whereas natriuretic peptide receptor B (NPR-B) stimulates long bone growth in a C-type natriuretic peptide-dependent manner. Many reports indicate that ATP is essential for NPR-A and NPR-B activation. Current models suggest that natriuretic peptide binding to receptor extracellular domains causes ATP binding to intracellular kinase homology domains, which derepresses adjacent catalytic domains. Here, we report 100-fold activation of natriuretic peptide receptors in the absence of ATP. Addition of a nonhydrolyzable ATP analog had no effect at early time periods (seconds) but increased cGMP production about two-fold after longer incubations (minutes), consistent with a stabilization, not activation, mechanism. These data indicate that ATP does not activate natriuretic peptide receptors. Instead, ATP increases activity primarily by maintaining proper receptor phosphorylation status, but also serves a previously unappreciated enzyme stabilizing function.