Arresting inflammation: contributions of plasma membrane and endosomal signaling to neuropeptide-driven inflammatory disease

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Although GPCR trafficking between plasma and endosomal membranes controls signaling, the importance this trafficking to complex patho-physiological processes, such as inflammation and pain, is unclear. Substance P (SP) binding to the neurokinin 1 receptor (NK$_1$R) promotes inflammation and pain. b-arrestins (bARRs) and endothelin-converting enzyme-1 (ECE-1) control the balance of NK$_1$R signaling between plasma and endosomal membranes. bARRs desensitize plasma membrane signaling and mediate endosomal signaling, whereas ECE-1 degrades SP in endosomes to attenuate endosomal signaling and to promote receptor recycling and resensitization of plasma membrane signaling. We examined the effects of ECE-1 and bARR disruption on SP inflammatory signaling in human colonocytes. SP induced translocation of bARRs to the plasma membrane, followed by bARR-dependent trafficking of the SP$\cdot$NK$_1$R$\cdot$bARR complex to ECE-1-containing endosomes. bARRs desensitized NK$_1$R Ca$^{2+}$ signaling at the plasma membrane. bARRs promoted, whereas ECE-1 attenuated, SP-dependent endosomal MAPK signaling. Conversely, both ECE-1 and bARRs mediated resensitization of NK$_1$R Ca$^{2+}$ signaling at the plasma membrane. SP-induced NF-kB activation and IL-8 expression were dependent on ECE-1 and bARR2, but did not require MAPK activation. Whereas ECE-1 inhibition attenuated colitis in mice, bARR2 deletion exacerbated the disease. Thus, the primary function of bARRs and ECE-1 in SP-dependent inflammatory signaling is to regulate NK$_1$R desensitization, internalization and recycling/resensitization, thereby promoting sustained NK$_1$R plasma membrane signaling that drives chronic inflammation.