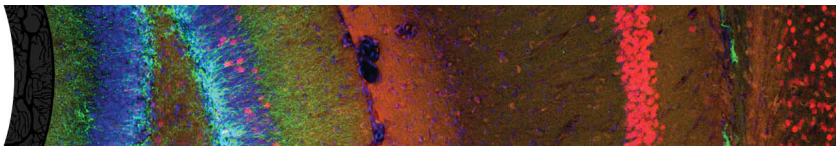
NEUROSCIENCE 2021
50TH ANNUAL MEETING



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Session P395 - Inflammatory Pain

Add to Itinerary

P395.02 - Rapgef Family Members Expressed In Mouse Dorsal Root Ganglion Neurons Contribute To Erk Phosphorylation Downstream Of G_s-coupled Receptors

November 11, 2021, 8:45 AM - 9:45 AM | Virtual Only

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Abstract
Members of the Rap guanine nucleotide exchange factor (Rapgef) family activate Rap/Ras signaling pathways by exchanging GTP for GDP. Four of the 6 Rapgefs have been identified as effectors of cAMP signaling: Rapgef2, Rapgef3/Epac1, Rapgef4/Epac2, and Rapgef6. Rapgef1(C3G) does not bind cAMP, but has been implicated in Protein Kinase A (PKA)-dependent ERK activation. ERK signaling is required for some components of nociceptor sensitization, therefore cAMP signaling to ERK may represent an important pathway in the induction of inflammatory hyperalgesia by G_s-coupled receptors (G_sPCRs). We recently identified a role for Epac2 in nociceptor sensitization and behavioral hyperalgesia evoked by prostaglandin E2 (PGE2). Epac signaling has been reported to be mediated by both Protein Kinase C (PKC) and ERK1/2. However, studies in heterologous systems suggest that activation of ERK downstream of G_sPCRs is mediated by Rapgef2, either alone or in combination with PKA. To examine these divergent signaling pathways downstream of G_sPCRs, we first tested the distribution of Rapgef family members in dorsal root ganglia (DRG) of male mice by qPCR. We found that all 6 Rapgefs are expressed in DRG, to varying degrees. Next, we examined the relative contributions of PKA and Rapgef2 in the activation (phosphorylation) of ERK (pERK) downstream of cAMP. Application of the cAMP analog 8-Br-cAMP to dissociated DRG neurons induced pERK. The Rapgef2-selective cAMP analog N^6-Phe-cAMP also showed a dose-dependent (150-1000 micromolar) induction of pERK. Co-application of 1mM SQ22356 (an inhibitor of Rapgef2) reversed the effect of N^6-Phe-cAMP, supporting the activation of ERK by Rapgef2. Next, we examined whether activation of endogenous receptors was capable of inducing pERK. To identify G_sPCRs highly expressed in DRG, we examined published RNA-seq data and then confirmed expression of beta-adrenergic receptors Adrb1-3 and dopamine receptors Drd1, 5 by quantitative PCR. Of these receptors, Adrb2 and Drd1 were the most highly expressed. Application of 10 micromolar isoproterenol (Adrb2) or 1 micromolar SKF38393 (Drd1/5), induced pERK by 360% or 160% above baseline, respectively. While PKA inhibitor peptide PKI reduced the effect of isoproterenol by ~50%, it only slightly reduced the effect of SKF38393. These results suggest that different G_sPCRs may be differentially coupled to Rapgef2. In conclusion, Rapgef1, 2, and 6 are expressed in DRG and may contribute to cAMP signaling to ERK downstream of G_sPCRs.