Differential mechanisms of vasodilation of PACAP and CGRP in rat middle meningeal artery: Potential role in migraine headache.

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Migraine is the most common incapacitating neurological disorder, characterized by an intense pulsating headache. The cellular mechanisms contributing to migraine headache are poorly understood, but a leading hypothesis is that prolonged dilation of cranial arteries, specifically the middle meningeal artery (MMA), is involved in the sensation of headache pain. The neuropeptides pituitary adenylate cyclase activating polypeptide (PACAP) and calcitonin gene-related peptide (CGRP) have been shown to potently dilate the MMA and induce migraine-like headaches. The mechanisms by which these peptides exert their effect on the MMA remain unclear. The goal of this study is to decipher the mechanisms of PACAP and CGRP-induced dilations using freshly isolated pressurized rat MMAs. At an intravascular pressure of 40 mmHg, MMAs developed myogenic tone (i.e. constricted) representing ~ 40 % decrease in diameter. Treatment of these arteries with PACAP (3 nM) or CGRP (1 nM) caused significant vasodilation (59 ± 5.8 % of maximum and 77 ± 4.01 % of maximum, respectively). PACAP-induced dilation was abolished in the presence of glibenclamide, an ATP-sensitive K⁺ (K\text{ATP}) channel blocker. However, CGRP-induced dilation remained unaffected by treatment with glibenclamide, alone. Paxilline, a blocker of large-conductance Ca²⁺-activated K⁺ (BK) channels, or 4-aminopyridine, a blocker of voltage-gated K⁺ (K\text{V}) channels also did not affect CGRP-induced MMA dilation. Further, CGRP-induced dilations were not altered by a combination of L-nitroarginine (L-NNA) to inhibit nitric oxide synthesis, indomethacin to inhibit prostacyclin synthesis, apamin to block endothelial small-conductance Ca²⁺-activated K⁺ channels and TRAM-34 to block endothelial intermediate-conductance Ca²⁺-activated K⁺ channels. Interestingly, CGRP-induced dilations were blocked by raising extracellular K⁺ to 30 mM, implicating involvement of K⁺ channel activation in the dilatory response of this peptide. Further, CGRP-induced dilations were abolished by a combination of compounds that included glibenclamide, paxilline, L-NNA, indomethacin, apamin, TRAM-34 and thapsigargin, an inhibitor of the sarco-endoplasmic reticulum Ca²⁺-ATPase. In summary, although PACAP and CGRP have been reported to increase adenyl cyclase activity, they act via distinct vasodilatory mechanisms in the MMA. PACAP induces vasodilation through K\text{ATP} channel activation, while CGRP appears to utilize multiple cell signaling pathways. By understanding the distinct mechanisms involved in MMA dilation caused by PACAP and CGRP it may be possible to develop new combination therapies for migraine headache.