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Pituitary Adenylate Cyclase-Activating Polypeptide plays an important role in nitroglycerol-induced trigeminovascular activation in mice

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Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP) and its receptors are present in sensory neurones and vascular smooth muscle. Its infusion triggers migraine-like headache in humans. Therefore, we aimed at examining the effects of PACAP in nitroglycerol (NG)-induced light-aversive behavior, meningeal vasodilatation and c-Fos expression in the trigeminal nucleus and ganglia using gene-deleted mice (PACAP^{-/-}). Significantly reduced light-aversive behaviour was detected in the modified light-dark box in PACAP^{-/-} mice both in the early phase (0-30 min) due to the acute vasodilating effect of NG (10 mg/kg i.p.) and in the late phase (90-120 min) when the trigeminal system is sensitized. NG produced significant (30-35%) biphasic increase of meningeal blood flow measured by laser Doppler imaging in anaesthetized mice with a second peak starting 170 minutes after its injection. In contrast, in PACAP^{-/-} mice NG did not alter microcirculation in the first 2 h-period and exerted only a minor increase later. Exogenous PACAP (300 mg/kg i.p.) produced 30% meningeal flow increase. C-Fos expression in the trigeminal ganglia and nucleus caudalis was also significantly smaller in PACAP^{-/-} mice. PACAP has both direct and indirect vasodilating effects on the brain surface, and also activates the trigeminovascular system involved in migraine. Exploration of its mechanism and targets might open interesting future perspectives in novel anti-migraine therapy.