Sir, The two peptides pituitary adenyl cyclase-activating polypeptide-38 (PACAP) and vasoactive intestinal polypeptide (VIP), given intravenously in humans, both dilate extracerebral cranial arteries, but only PACAP38 (Schantz et al., 2009)—not vasoactive intestinal polypeptide (Rahmann et al., 2008)—induces migraine-like attacks in patients with migraine. Possible mechanisms for the difference in migraine induction were investigated in a recent crossover study in which 16 of 24 patients with migraine developed migraine after intravenous PACAP infusion, and vasoactive intestinal polypeptide infusion induced migraine in 4 of 24 patients (Amin et al., 2014). Magnetic resonance angiography showed dilatation of the superficial temporal artery and the extracranial part of the middle meningeal artery after both polypeptides whereas there was no effect on the middle cerebral artery with either polypeptide (Amin et al., 2014). The vasodilatation of the superficial temporal artery and middle meningeal artery was the same for both polypeptides after 20 min but only persisted after 2 h for PACAP38. The migraine-like attacks were treated effectively with subcutaneous sumatriptan (n = 6) and this was associated with a constriction of superficial temporal artery and middle meningeal artery but not middle cerebral artery (Amin et al., 2014).

The authors discuss several possible explanations for the difference in migraine induction, including prolonged dilatation of extracerebral arteries combined with sensitization of trigeminal perivascular afferents (Amin et al., 2014).

The authors note that:

1PACAP38 and VIP receptors are present in cerebral and extracranial arteries (Knutsson and Edvinsson, 2002; Chan et al., 2011), but neither exogenously administered PACAP38 nor VIP caused dilatation of cerebral arteries, suggesting no passage of the peptides across the blood–brain barrier during the experiment. Previous in vitro studies of rat and human cerebral arteries showed that abluminal, but not luminal application of PACAP38 and VIP caused relaxation of smooth muscle cells of the rat middle cerebral artery (Grände et al., 2012). Collectively, these data suggest that central effects of PACAP38 and VIP after systemic administration are unlikely in the human being (Amin et al., 2014).

Also in a previous study with healthy volunteers, the middle meningeal artery but not the middle cerebral artery, was dilated after PACAP38 infusion (Amin et al., 2012).

The presence of receptors for both polypeptides in both extracerebral arteries (middle meningeal artery) and cerebral arteries (middle cerebral artery) combined with an effect on only middle meningeal artery in vivo suggests a barrier between the blood and the muscle cells of the tunica media of the middle cerebral artery. The authors suppose that this presumed barrier, observed with both these polypeptides in man (no effect on middle cerebral artery) (Amin et al., 2012, 2014) and rat (no effect on middle cerebral artery with luminal administration of PACAP38) (Grände et al., 2012) has the same attributes as the blood–brain barrier, and therefore state that central effects of PACAP38 and vasoactive intestinal polypeptide are unlikely (Amin et al., 2014).

Lack of effect of a substance with possible vascular effect on middle cerebral artery (indicating a barrier), however, needs not predict no transport of the substance across the blood–brain barrier. Thus luminal application of PACAP38 in rat middle cerebral artery in vitro did not dilate the artery (Grände et al., 2012). In contrast, PACAP38 crosses the blood–brain barrier in rat by a specific, saturable mechanism (Banks et al., 1996). PACAP is transported across the blood–brain barrier as an intact peptide to enter the parenchymal space of the brain (Banks et al., 1996). The amount entering the whole brain is only moderate: the per cent intravenous (iv) dose taken up per gram of brain (%iv/g) is only 0.118%, but this is six times more than the %iv/g (0.02%) for morphine (Banks et al., 1996). The amount of PACAP38 entering the brain is sufficient to exert neuroprotection in vivo in animal studies (Brenneman, 2007). Vasoactive intestinal polypeptide...
crosses the blood–brain barrier in mice by transmembrane diffusion (Dogrukol-Ak et al., 2003) and is also a neuroprotector, but it is generally 100–1000 times less potent than PACAP38 in producing neuroprotection in the brain (Brenneman, 2007).

A possible passage of PACAP and vasoactive intestinal polypeptide across the human blood–brain barrier has not been investigated, but animal studies suggest that such an effect could be present (Banks et al., 1996; Dogrukol-Ak et al., 2003); and the lack of an effect of the two polypeptides on the middle cerebral artery in patients with migraine (Amin et al., 2014) most likely does not exclude such an effect, confer the results in rats (Banks et al., 1996; Grände et al., 2012). In animal studies PACAP and vasoactive intestinal polypeptide have different neuroprotection potency (Brenneman, 2007), and could be different for other brain effects. This could theoretically explain the observation (Amin et al., 2014) that the two vasodilators dilate the extracerebral arteries to the same extent (but with different duration) but only one of these (PACAP) induces migraine-like attacks. I suggest that the possibility of a central effect of migraine-inducing drugs and substances should be investigated further. For nitroglycerin-induced migraine-like attacks in a subset of patients with premonitory symptoms after nitroglycerin, it was recently shown in a PET study that there is brain activation in several regions including the hypothalamus in the premonitory phase (Maniyar et al., 2014).

The problem of the exact site of action of PACAP in this human migraine model should be fully elucidated before considering development of e.g. a specific PAC1 receptor antagonist for human use with the perspective of possible later therapeutic use in migraine.

References
Dogrukol-Ak D, Banks WA, Tuncel N, Tuncel M. Passage of vasoactive intestinal peptide across the blood-brain barrier. Peptides 2003; 24: 437–44.