CGRP outflow from the meninges into blood and cerebrospinal fluid

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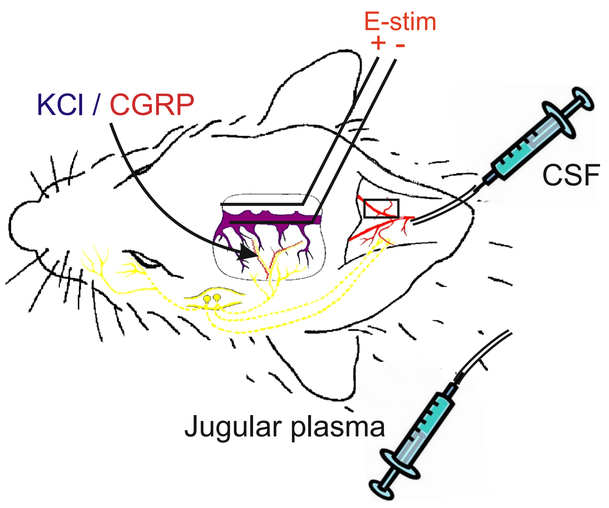
Objective

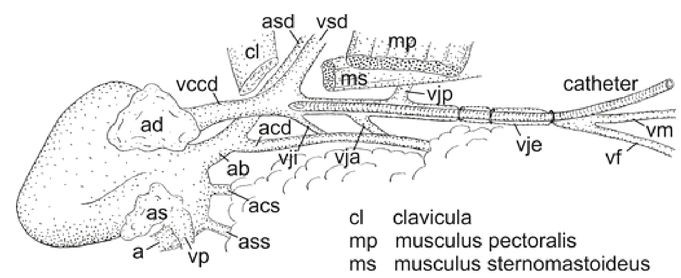
Calcitonin gene-related peptide (CGRP) has frequently been detected in the blood of the jugular vein at increased concentrations during migraine and cluster headache. Few CGRP measurements have been reported in peripheral blood and cerebrospinal fluid (CSF). Perivascular trigeminal, particularly meningeal afferents are considered as the source of CGRP (Fig 4). In an animal model we aimed to understand the pathways of CGRP outflow into the circulation and CSF.

1A.



Stimulation of the cranial dura mater (E-stim, KCl), application of CGRP and sampling of CSF and plasma

B.



cl	clavicula
mp	musculus pectoralis
ms	musculus sternomastoideus

a	aorta
ab	arteria brachiocephalica
acd	arteria carotis dextra
acs	arteria carotis sinistra
ad	auricula dextra
as	auricula sinistra
asd	arteria subclavia dextra
ass	arteria subclavia sinistra

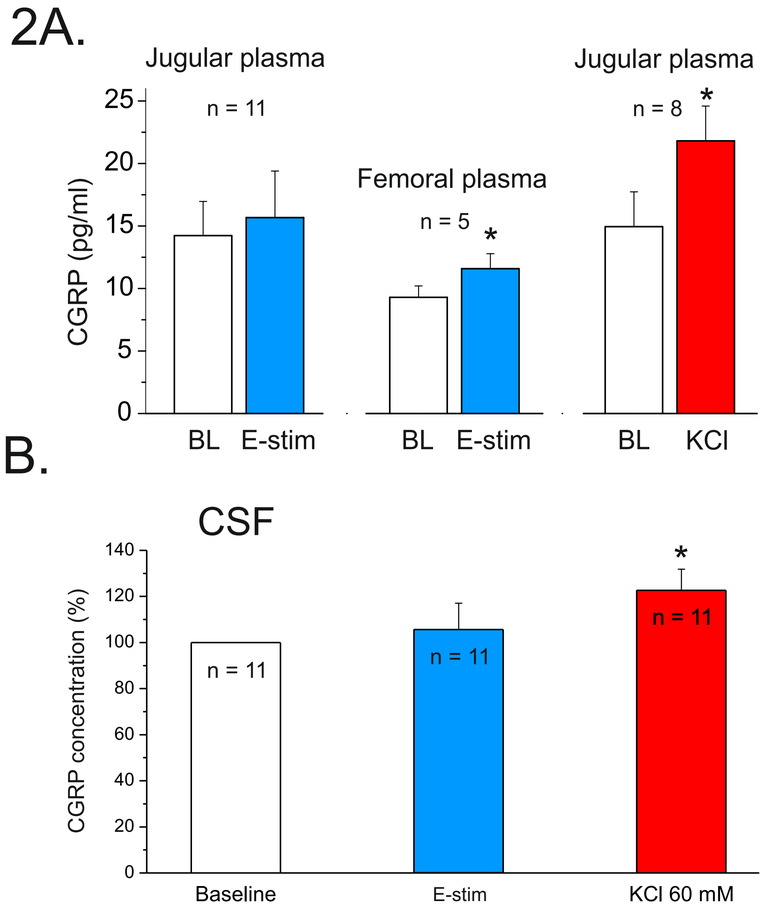
vccd	vena cava cranialis dextra
vf	vena facialis
vja	vena jugularis anterior
vje	vena jugularis externa
vji	vena jugularis interna
vjp	vena jugularis posterior
vm	vena maxillaris
vp	vena pulmonaris
vsd	vena subclavia dextra

Position of the catheter in the external jugular vein

Methods

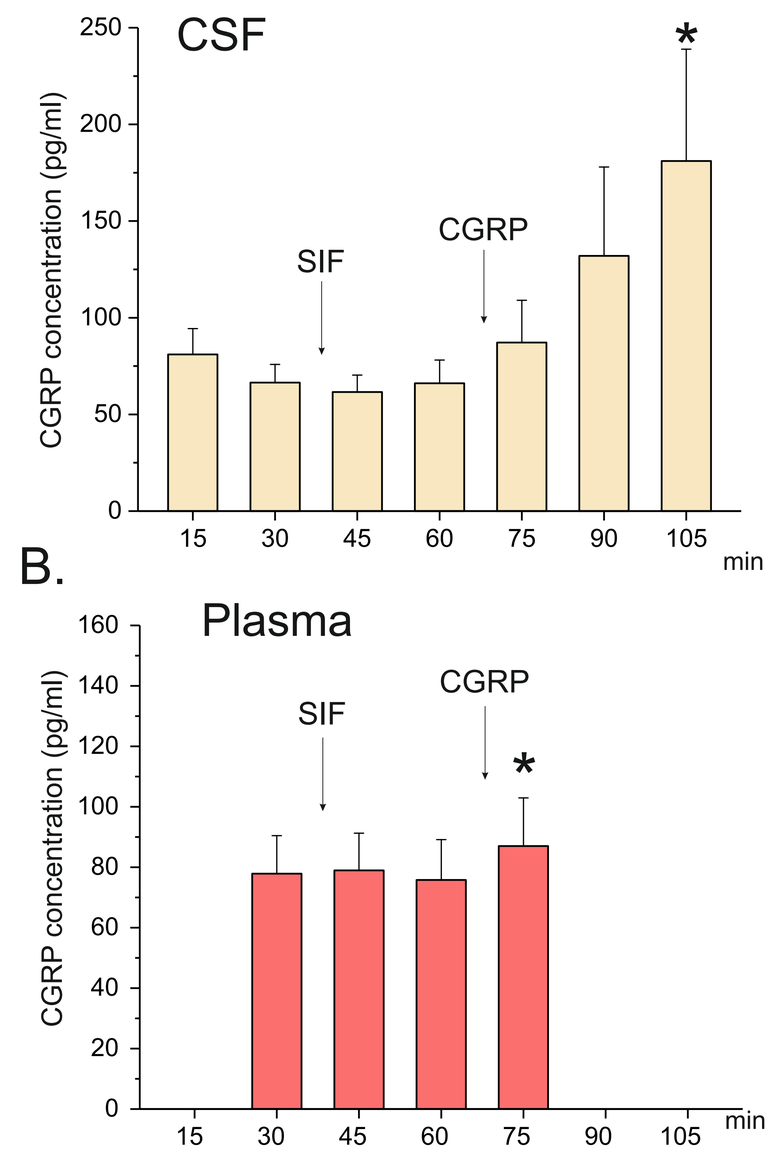
In adult anaesthetized Wistar rats, a catheter was introduced into the right external jugular vein in caudal direction (Fig 1B). Blood and CSF were collected from the jugular vein or the femoral artery and the cisterna magna. CGRP was measured in plasma and CSF using an ELISA. The parietal dura mater was stimulated electrically or with depolarizing concentrations of KCl (60 mM). Changes in CGRP content of jugular venous blood and CSF samples upon CGRP (10 µM) application onto the exposed dura mater were also measured (Fig 1A).

2A.



CGRP concentrations measured in the jugular or femoral plasma and in CSF after electrical (E-stim) or chemical (KCl) stimulation of the dura mater.

3A.



CGRP concentrations measured in the CSF (A) and jugular plasma (B) after application of CGRP on the dura mater (SIF: synthetic interstitial fluid).

Results

Electrical stimulation of the dura mater with C-fibre strength was followed by a moderate increase in CGRP in the blood of the jugular vein at the branching point of the external and the internal jugular vein 10 min after stimulation. The CGRP concentration was comparable to that collected from the right femoral artery (Fig 2A). In contrast, significant increases in CGRP concentrations were measured in the jugular vein and CSF after application of the depolarizing KCl to the dura mater (Fig 2A,B). Direct application of CGRP onto the dura mater was followed by a slight increase in CGRP concentration in the jugular vein and a significant but delayed increase in the CSF (Fig 3A,B).

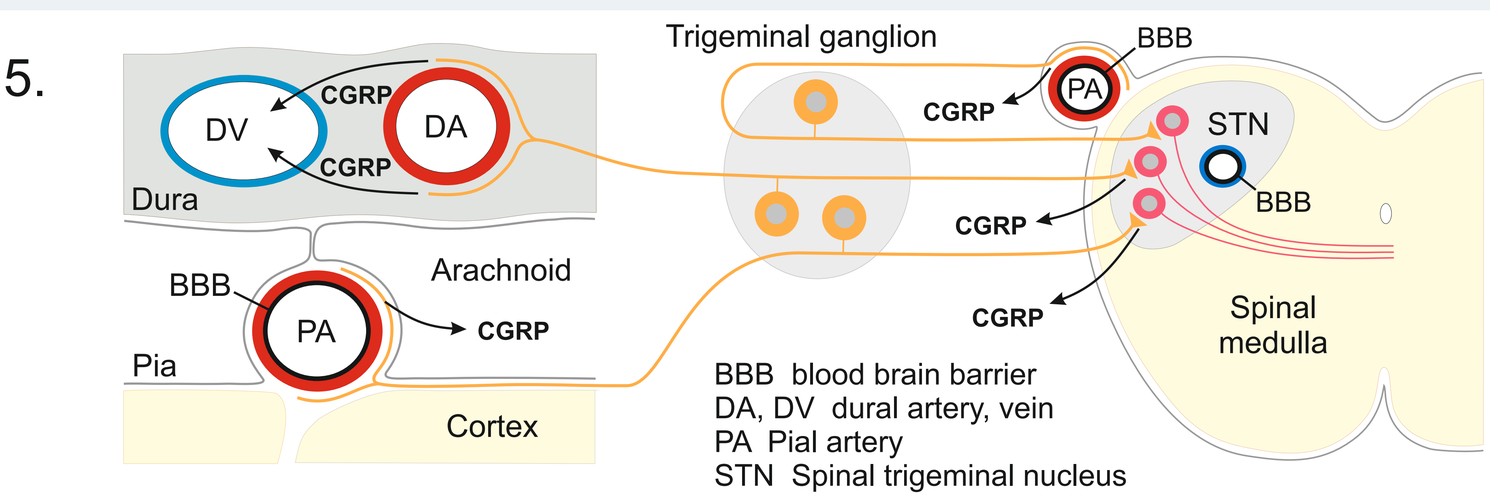
4.

Photomicrograph showing the distribution of CGRP-immunoreactive afferents in the rat dura mater (MMA: meddle meningeal artery).

Conclusion

CGRP released from trigeminal afferents (Fig 4) in the dura mater is mainly taken up from venous vessels and flowing out via the jugular veins. However, the collection of CGRP from the branching point of external and internal jugular vein may be insufficient, because in rat the internal jugular vein conducts very little venous blood. The increasing concentration of CGRP in the CSF may be due to the release from medullary sources during stimulation and slow diffusion from the dura mater into the subarachnoid space (Fig 5).

5.



Release of CGRP from trigeminal afferents and its proposed drainage in the meningeal tissues.