SOCIETÀ ITALIANA DI FARMACOLOGIA

MODELLO PER INVIO RELAZIONE DI METÀ E FINE PERIODO

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TIPOLOGIA DI BORSA RICEVUTA: Borsa per soggiorno all'estero

TIPOLOGIA DI RELAZIONE: Metà periodo

TITOLO DELLA RELAZIONE: "Involvement of Prokineticin System in an animal model of migraine"

RELAZIONE:

Migraine is one of most prevalent and disabling disorder in the world, the onset mechanisms are still not entirely clear but multiple hypotheses have been proposed, including cortical spreading depression, vasodilation, plasma protein extravasation and sensitization of nociceptive dural afferents[1;2]. Several studies have recognised the involvement of the trigeminal vascular system and of the neurotransmitter calcitonin gene related peptide (CGRP, a potent vasodilator).[3;4] Indeed, when the cranial blood vessels are dilated, there is activation of perivascular trigeminal sensory nerve fibres and a pain response is conveyed to the brainstem (and from there to higher brain centres) and vasoactive peptides (such as substance P and CGRP) are released from trigeminal fibres. These peptides exacerbate vasodilation and cause neurogenic inflammation. Both vasodilation and neurogenic inflammation increase activation of the sensory trigeminal fibres, perpetuate the release of vasoactive peptides and modulate transmission of pain impulses to the brain[5]. Moreover, blood levels of CGRP are elevated during migraine attacks[6] and intravenous administration of CGRP[7] or other vasodilators such as nitric oxide (NO) donor[8] are known to induce migraine headache in migraineurs, but not in controls.

Triptans are a family of drugs used for the acute treatment of migraines and cluster headaches. In patients with headaches, the frequent use of triptans (such as sumatriptan) can lead to medications overuse headache (MOH), a condition of major risk for the transformation of episodic headache to chronic

migraine. It is believed that these drugs may induce neural adaptations in the trigeminal afferents that lower the thresholds to stimuli that trigger migraine headache.[9]

Prokineticin 2 (PK2) and its receptors (PKR1 and PKR2) are proteins belonging to the Prokineticin (PK) family. PKRs are expressed in the peripheral and central nervous system and PK2 is important for nociceptor activation. Indeed, administration in rodents of Bv8 (the amphibian analogue of PK2) induces a significant decrease in sensory thresholds to noxious thermal or mechanical stimuli[10] and directly evokes the release of CGRP in spinal cord, dorsal root ganglia[11] (DRG) and in the trigeminal ganglia[12].

In primary DRG neurons cultures, we have previously demonstrated that TRPV1 (transient receptor potential cation channel subfamily V member 1, receptor involved in nociception) co-localize with PKR1 (68% of TRPV1 expressing neurons) and PKR2 receptors (about 10% of TRPV1 expressing neurons) and PKR1 null-mutant mice show impaired nociceptive response to mechanical and thermal stimuli compared to wild- type mice but not in tactile allodynia,[13] so we supposed that PKR2 is involved in tactile allodynia. Animals with neuropathic pain induced by Chronic Constriction Injury showed increased PKR2 expression in nociceptors and in the spinal cord neurons, together with increased expression of PK2, which is crucial for the induction and maintenance of tactile allodynia.[14]

The aim of my research at University of Sheffield is to study the involvement of the Prokineticin System in an animal model of migraine, developed by Dr. De Felice.[15]

In this animal model, rats received sumatriptan by osmotic minipumps for 6 days; rats develop cephalic and extracephalic allodynia during sumatriptan infusion and a state of “latent sensitization”, which manifests with increased sensitivity to migraine triggers, once sumatriptan is not longer in the system: for this reason, at day 20, rats received an injection of Sodium Nitroprusside (SNP, a migraine trigger[16]) to induce cutaneous allodynia.

At day 6 and day 20 after surgery, rats were sacrificed and tissues were quickly collected and stored at -80° C until their use. I performed qPCR on brainstem, trigeminal ganglia and dura mater (three areas involved in migraine) to analyse the mRNA expression levels of PK2, PKR1, and PKR2. In the brainstem, as well as in the trigeminal ganglia and in the dura mater there were not statistically significant changes in PK2, PKR1 or PKR2 mRNA expression levels between saline and sumatriptan pre-exposed rats at both day 6 or day 20 (with SNP injection).

My future aims will be analyse proteins expression and distribution of PK2 and its receptors in trigeminal ganglia and brainstem by western blot or immunofluorescence assays; probably, mRNA and proteins expression could be different.

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