Migraine - acute therapy

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LASMIDITAN INHIBITS DURAL CGRP RELEASE FROM THE RAT TRIGEMINOVASCULAR SYSTEM

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Introduction: Migraine is associated with activation of the trigeminovascular system, resulting in release of calcitonin gene-related peptide (CGRP) and dysfunctional nociceptive transmission. Intravital microscopy of a closed cranial window in rats is a well-established model to study activation of the trigeminovascular system and neurogenic dural inflammation. Lasmiditan is a novel, selective 5-HT_{1F} receptor agonist recently developed for the acute treatment of migraine. While lasmiditan has been efficacious in clinical trials, the exact mechanism of action has not been completely elucidated. Previous ex-vivo studies have shown that lasmiditan can inhibit CGRP release from mouse dura, trigeminal ganglion and trigeminal nucleus caudalis.

Objectives: The present study investigated the effects of lasmiditan (and thus the role of 5-HT_{1F} receptor agonism) in the modulation of peripheral trigeminal CGRP release from trigeminal afferents in the dura of anesthetized rats.

Methods: Male Sprague-Dawley rats (n=54) were anesthetized and the parietal bone was thinned to visualize and measure the middle meningeal artery diameter using intravital microscopy. Vasodilator responses to endogenous (released by 10 µg/kg i.v. capsaicin or 150-250 µA periarterial electrical stimulation) or exogenous (1 µg/kg i.v. bolus) CGRP were elicited in the absence or presence of intravenous vehicle, sumatriptan or lasmiditan (0.3, 1, 3 and 10 mg/kg).

Results: The administration of lasmiditan (0.3-10 mg/kg), as well as the higher doses of sumatriptan (3-10 mg/kg) significantly and dose-dependently attenuated ($P<0.05$) endogenous CGRP release, but not the effects of exogenous CGRP. Additionally, in contrast to sumatriptan, lasmiditan did not affect blood pressure effects *per se* at any of the doses tested.

Conclusion: In addition to peripheral and central antinociceptive mechanisms (since lasmiditan can cross the blood-brain barrier), inhibition of dural CGRP release from peripheral trigeminal afferents may contribute to lasmiditan's efficacy for the treatment of migraine attacks

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