Pharmacology Discovery Services

A Eurofins Discovery Partner Lab

Migraine Model for *In Vivo* Studies

Evaluation of anti-migraine therapeutics using the rodent capsaicin-induced dermal blood flow (CIDBF) model

Migraine

Migraine is a neurological disorder characterized by recurring headaches that can be moderate to severe in intensity. Migraine is typically pulsating or throbbing in nature and often affects one side of the head. It is often accompanied by nausea, vomiting, and sensitivity to light and sound. Migraine can last for hours and even days and can be triggered by factors such as stress, hormonal changes, certain foods, and lack of sleep.

Migraine affects about 12% of the global population, making it one of the most common neurological disorders worldwide. It is more prevalent in women than men, with a female-to-male ratio of approximately 3:1. The onset of migraine occurs at any age but is most commonly reported in individuals between the ages of 15 and 55. Migraine significantly impacts an individual's quality of life and may require medical management to control symptoms and prevent future attacks. In 2021, medications for migraine were estimated to value USD 4.4 billion.

Although the pathophysiology of migraine is not clearly understood, extensive research from the last three decades demonstrated that calcitonin gene-related peptide (CGRP) plays a crucial role in the development of migraine. Increased levels of CGRP can induce inflammation and cause dilation of blood vessels in the brain, leading to the characteristic pain and other symptoms associated with migraine. Drugs that target CGRP or its receptors, the CGRP inhibitors, have been developed as a new class of treatment for migraine. Compared to the old therapies, CGRP inhibitors are more effective in reducing the frequency and severity of migraine with fewer side effects. Indeed, since 2018 the FDA has approved seven new CGRP inhibitors for migraine therapy.

Capsaicin-induced Dermal Blood Flow (CIDBF) in Rats

Capsaicin is a type of vanilloid receptor agonist, which binds to and activates the transient receptor potential vanilloid subtype 1 (TRPV1) involved in the perception of pain, heat, and inflammation. The binding of capsaicin to TRPV1 leads to the release of neuropeptides from neurons, including calcitonin gene-related peptide (CGRP), substance P, and neurokinin A, further causing vasodilation.

Capsaicin-induced dermal blood flow (CIDBF), a method used to measure blood flow in the skin after the application of capsaicin, is a well-established biomarker for evaluating therapeutics for migraine. In the CIDBF model, a small amount of capsaicin is applied topically to the skin, and the blood flow in the treated area is measured using various techniques, such as laser Doppler imaging or laser speckle contrast imaging. This model is commonly used to evaluate the efficacy of drugs or other interventions in modulating vasodilation and blood flow in the skin. It is also applied in clinical studies to investigate the role of CGRP and other neuropeptides in various conditions, including migraine.

PDS offers CIDBF measurement as the readout using male Lewis rats. Following measurement of the basal dermal blood flow (DBF) by Laser Doppler Imager (Moor Instruments, LDI2-IR) in the abdominal skin region of the testing subject, capsaicin at 2 mg/site, is applied on two sites within two rubber O-rings, each 3 mm in diameter, placed on each side of the shaved abdomen under anesthesia to induce the increase of blood flow. The treatment time point, dosage, and administration route can be tailored to meet therapeutic needs. Consecutive measurements of DBF are taken for 25 minutes following the capsaicin challenge. The % DBF increase over the baseline is calculated in each animal. Ubrogepant, a clinically approved drug, is used as a reference control and administered at 5 mg/kg by a single intravenous (IV) injection 10 minutes before topical capsaicin stimulation. Inhibition of capsaicin-induced increase in blood flow is considered a significant anti-migraine effect.

To learn more about our pain-model capabilities, contact PDS. And optional endpoints, including terminal plasma, brain, and other tissue collection for further analysis, are also available upon request.

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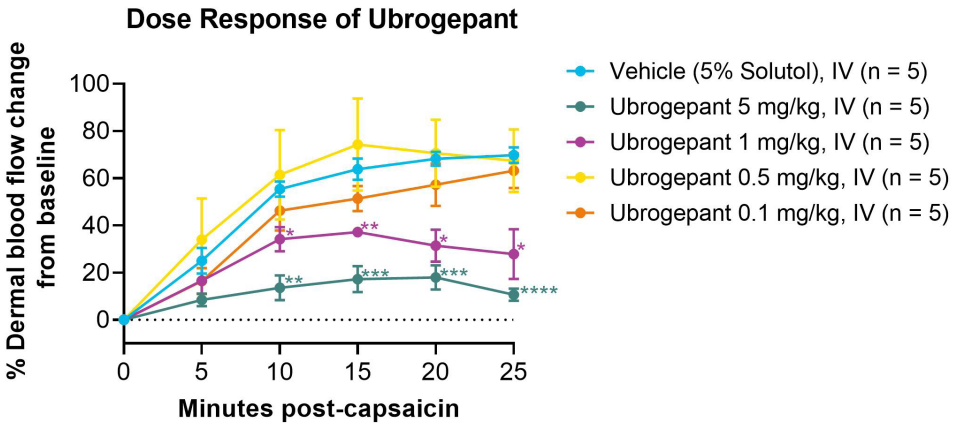

Data are shown in mean ± S.E.M.

* or ** or *** or **** represent $p < 0.05$ or $p < 0.01$ or $p < 0.001$ or $p < 0.0001$, respectively, by repeat measure two-way ANOVA followed by Dunnett's post-hoc analysis comparing to Vehicle.

Figure 1. Representative data of migraine model using CIDBF.
Capsaicin was applied to euthanized animals as described. Ubrogepant, at 5, 1, 0.5, and 0.1 mg/kg, is administered by a single intravenous injection 10 min before topical capsaicin stimulation. DBF measurement by Laser Doppler Imager was conducted every 5 min. from 0 min. (pre-capsaicin) until 25 min. after topical capsaicin stimulation.

Recommended Study Design

Group	Description	Treatment	Route	Dosage	Frequency	Group Size
1	Sham, no capsaicin	Vehicle	PO	5 mL/kg	QD	4
2	Vehicle control	Vehicle	PO	5 mL/kg	QD	8
3	Test group	TA-1	PO	Low	QD	8
4	Test group	TA-1	PO	Mid	QD	8
5	Test group	TA-1	PO	High	QD	8
6	Positive control group	Ubrogepant	IV	5 mg/kg	QD	8
Total number of animals						44

Table 1. Recommended study design. Note the route, dosage, and frequency can be tailored according to the sponsor's request.

References

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3. Benschop RJ, *et al.* Development of a novel antibody to calcitonin gene-related peptide for the treatment of osteoarthritis-related pain. *Osteoarthritis Cartilage.* 2014 Apr;22(4):578-85. doi: 10.1016/j.joca.2014.01.009. PMID: 24508775. https://pubmed.ncbi.nlm.nih.gov/24508775/

For more information on Pain Model Capabilities, please visit:
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