DEVELOPMENT OF KAPPA OPIOID RECEPTOR ANTAGONISTS FOR PROPHYLACTIC TREATMENT OF MIGRAINE

By

LARRY ROBERT FRANK JR.

A Thesis Submitted to The Honors College

In Partial Fulfillment of the Bachelor's degree

With Honors in

Physiology

THE UNIVERSITY OF ARIZONA

MAY 2014

Approved by:

Frank Porreca

Dr. Frank Porreca
Department of Pharmacology

The University of Arizona Electronic Theses and Dissertations
Reproduction and Distribution Rights Form

The UA Campus Repository supports the dissemination and preservation of scholarship produced by University of Arizona faculty, researchers, and students. The University Library, in collaboration with the Honors College, has established a collection in the UA Campus Repository to share, archive, and preserve undergraduate Honors theses.

Theses that are submitted to the UA Campus Repository are available for public view. Submission of your thesis to the Repository provides an opportunity for you to showcase your work to graduate schools and future employers. It also allows for your work to be accessed by others in your discipline, enabling you to contribute to the knowledge base in your field. Your signature on this consent form will determine whether your thesis is included in the repository.

Name (Last, First, Middle)

Frank Jr., Larry Robert

Degree title (eg BA, BS, BSE, BSB, BFA):

BSHS

Honors area (eg Molecular and Cellular Biology, English, Studio Art):

Physiology

Date thesis submitted to Honors College:

May 1, 2014

Title of Honors thesis: Development of Kappa Opioid Receptor Antagonists For Prophylactic Treatment of Migraine

The University of Arizona Library Release Agreement

I hereby grant to the University of Arizona Library the nonexclusive worldwide right to reproduce and distribute my dissertation or thesis and abstract (herein, the "licensed materials"), in whole or in part, in any and all media of distribution and in any format in existence now or developed in the future. I represent and warrant to the University of Arizona that the licensed materials are my original work, that I am the sole owner of all rights in and to the licensed materials, and that none of the licensed materials infringe or violate the rights of others. I further represent that I have obtained all necessary rights to permit the University of Arizona Library to reproduce and distribute any nonpublic third party software necessary to access, display, run or print my dissertation or thesis. I acknowledge that University of Arizona Library may elect not to distribute my dissertation or thesis in digital format if, in its reasonable judgment, it believes all such rights have not been secured.

☑ Yes, make my thesis available in the UA Campus Repository!

Student signature: Larry Frank Date: 4/30/2014

Thesis advisor signature: Frank Porreca Date: 4/30/2014

☐ No, do not release my thesis to the UA Campus Repository.

Student signature: _____ Date: _____

Last updated: 04/01/13

Abstract

A common migraine trigger is stress. Exactly how stress produces migraine and its associated symptoms is not known. Remarkably, the kappa opioid receptor (KOR) system has been implicated as a critical link in the consequences of stress. Thus, blockade of the KOR could prevent stress induced migraine. We have used a preclinical model of stress-induced cephalic pain that mimics clinical observations of medication overuse headache (MOH). MOH results from overuse of drugs used to treat migraines, including triptans. MOH patients show increased sensitivity to triggers of migraine, including stress. Treatment of rats with triptans produces similar increased sensitivity to migraine triggers. Rats pretreated with triptans received a bright light stressor and developed cephalic pain that was reversed by systemic CYM51317, a KOR antagonist. Additionally, intracerebroventricular (ICV) administration of a KOR antagonist reversed the consequences of stress in these animals. Studies are now investigating whether the sustained administration of KOR antagonist can prevent the development of increased sensitivity to migraine triggers in animals pretreated with triptan drugs. The goal of these studies is to determine if the KOR is a viable target for the development of prophylactic migraine therapies.

Introduction

Migraine is a common debilitating disorder that is often associated with episodic, unilateral throbbing cephalic pain with and without aura, and may be accompanied by nausea and hypersensitivity to external stimuli including light and sound.[23,27] Migraine pain and associated symptoms can occur in the absence of injury. Although several mechanisms have been proposed, the underlying pathophysiology of migraine is not well understood. Migraine pain is thought to originate with the activation of trigeminal nociceptive afferents innervating the cranial meninges and cerebral blood vessels.[23,27] Sensitization of central and peripheral trigeminovascular neurons is hypothesized to be the source of the pain and processes leading to cephalic and non-cephalic cutaneous allodynia that is often observed with migraine.[4–6,11,19,25]

Only one class of medications specific for the treatment of migraine, triptans, has been developed and approved over the past several decades.[12] Triptans are agonists of $5HT_{1B/1D}$

presynaptic receptors on trigeminal afferents and are frequently prescribed as an acute therapeutic medication.[4,11] At least 95% of migraine sufferers regularly use acute medications or combination of medications.[21] Pharmacological therapy of migraine can be abortive or preventive (prophylactic). Abortive treatments include tripans and opioids, which should not be used more than 2-3 days a week. The frequent overuse of triptans can lead to medication overuse headache (MOH)[13,15,24] and is a major risk for the transformation of episodic to chronic migraine.[1] MOH is defined by the International Headache Society as more than 15 migraine headaches a month during regular acute medication overuse (more than 15 times per month) for a period of time lasting at least 3 months.[24] MOH may be associated with the presence of cutaneous allodynia, which may be a clinical marker of central sensitization.[6,10,21]

Initiation of a migraine attack is frequently associated with a variety of internal and external triggers such as stress, hormonal fluctuations, and sensory overload**.**[20,23] Stress, including psychological and environmental stress, is the most commonly reported trigger for migraine,[17,20] but it is not known how exactly stress may trigger migraine. For the treatment of stress- and mood-related disorders, the dynorphin/kappa opioid receptor (KOR) system appears to be a potential therapeutic target.[8] A CRF-dynorphin-KOR pathway has been hypothesized which may be an important mediator of stress responses, with the KOR playing a key role.[28] The KOR is expressed in several brain structures involved in reward modulation, mood state, and cognitive function including the prefrontal cortex, hippocampus, hypothalamus, and thalamus in both human and rat brains.[8,16,18,22] Mounting evidence has demonstrated that stress activates the dynorphin/KOR system in several brain regions,[2,8,18] which in turn has been shown to increase hypothalamic-pituitary-adrenal (HPA) axis activity.[7]

In this study, we tested the efficacy of KOR antagonists as either an abortive or a prophylactic treatment using a preclinical model of stress-induced pain that mimics MOH in humans. We hypothesized that administration of KOR antagonists after bright light exposure would reverse stress-induced allodynia. Additionally, we hypothesized that systemic co-infusion of a KOR antagonist with sumatriptan would prevent the development of sumatriptan-induced sensitization and resulting stress-induced allodynia.

Methods

Animals

Adult male Sprague Dawley rats (starting at 175-200g) were maintained in a climate-controlled room on a 12-hour light/dark cycle with food and water ad libitum. Testing was done in accordance with specifications of the International Association for study of Pain and the NIH guidelines for the handling and use of laboratory animals under protocols approved by the Institutional Animal Care and Use Committee of the University of Arizona.

Surgical Preparation

Stereotaxic surgeries were performed in anesthetized rats (i.p. ketamine/xylazine 80/12 1mg/kg). Guide cannulae were implanted toward the intracerebroventricular (ICV) for drug microinjections (right handed stereotaxis; from bregma: AP -1.0 mm, ML +1.8 mm, DV -3 mm from skull**)**. Gentamycin (1mg/kg) was given after surgery followed by a 7 day recovery period. Rats were individual housed after surgery.

Drug administration

Subcutaneous drug infusion was performed with Alzet osmotic mini-pumps (Alzet, Cuptertino CA, USA; model 2001) with a flow rate of 1 μl/h for 7 days. The mini-pumps were implanted subcutaneously in rats under anesthesia with isoflurane; the day of the implantation was considered day 0. The drugs administered by mini-pump infusion were sumatriptan (0.6 mg/kg/day) and/or CYM51317 (5 mg/kg/day). Acute CYM51317 administration was given orally (20 mg/kg, p.o.). Brain microinjections of zyklophin (3 nmol, ICV) were made through injectors extending 1mm beyond the guide cannula.

Bright Light Stress

Rats were placed in clear cages and exposed to bright light for 1 hour on days 20 and 21 from pump implantation. Lights were positioned at a sufficient distance to avoid temperature changes in the box.

Evaluation of Tactile Sensitivity

Somatosensory thresholds to tactile stimuli were determined by the application of von Frey filaments perpendicularly to the periorbital region and plantar surface of the hind paw, held for 3-6 seconds or until a withdrawal response was elicited (positive response). Baseline withdrawal thresholds were determined prior to mini-pump implantation. The rats were individually placed in clear cages and were allowed to acclimatize in a quiet environment for at least 30 minutes before testing. Maximum filament strengths were 8g and 15g for the periorbital region and hindpaw, respectively. Thresholds were determined by Dixon's up-down method.[9]

Statistical analyses

Behavioral changes from baseline to D6 within groups were analyzed using a paired t-test. Behavioral data between treatment groups and over time were analyzed by 2-factor analysis of variance (ANOVA). One-factor ANOVA followed by least significant difference test was used for behavioral changes from baseline values.

Results

Systemic CYM51317 co-infusion with sumatriptan prevents development of allodynia

CYM51317, a KOR antagonist, was co-infused with sumatriptan in separate mini-pumps. Sumatriptan co-infused with saline produced significant reductions in periorbital ($T_{(7)}$=3.579; p=0.009) and hindpaw ($T_{(7)}$=4.613; p=0.0024) thresholds at D6 post pump implantation. Baseline values were at 15$\pm$0.0g and 8$\pm$0.0g for the hindpaw and periorbital regions, respectively. On D6, withdraw thresholds had dropped to 9.71$\pm$1.15g and 6.13$\pm$0.52g (Fig 1). Co-infusion of sumatriptan with CYM51317 did not produce any reductions in allodynic thresholds. Co-infusion of CYM51317 with saline did not produce any significant changes in periorbital or hindpaw thresholds. Sensory thresholds for all groups remained at or returned to pre-pump implantation baseline levels within 20 days after implantation.

On D20 and D21, rats were exposed to a bright light stressor (BLS) for 1 hour. The 1st BLS induced mild facial and hindpaw allodynia, which became more profound after the 2nd BLS

exposure on D21 in sumatriptan/vehicle pre-exposed rats. The allodynia peaked at 2-3 hours post-stress, thresholds being significantly reduced from pre-BLS values for both periorbital region ($F_{(1,69)}$=16.48; p<.001) and hindpaw ($F_{(1,69)}$=34.17; p<.001). Periorbital withdrawal thresholds dropped from 8±0.0g pre-BLS to 5.88±0.72g 3 hours post-BLS and hindpaw thresholds dropped from 15±0.0g pre-BLS to 10.76±1.46g (Fig 2). Co-infusion of CYM51317 with sumatriptan prevented the development of stress-induced allodynia in both the periorbital and hindpaw regions on both days, with thresholds only dropping to 6.98±0.56g and 13.24±0.823g, respectively, at the lowest points. Co-infusion of either CYM51317 or vehicle with saline did not show any significant reductions in sensory thresholds in response to the BLS (Fig 2).

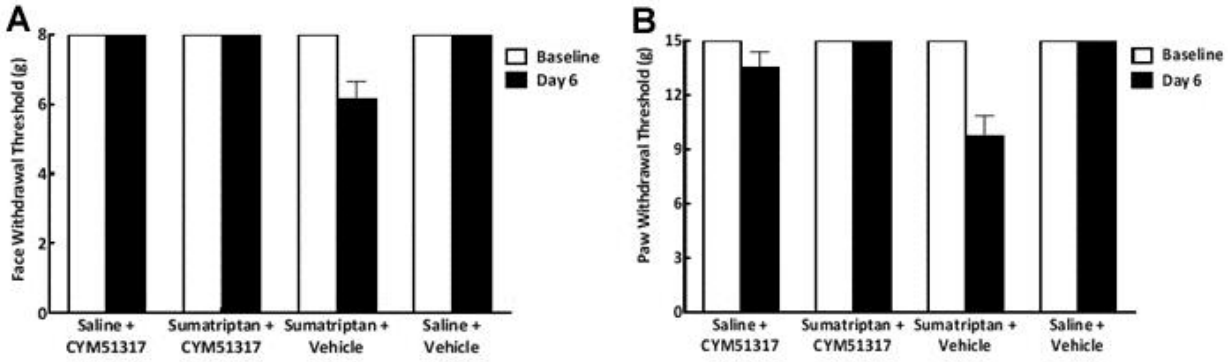

Figure 1: Sustained exposure to sumatriptan (0.6 mg/kg/day) co-infused with vehicle significantly (p<0.05) reduced withdrawal thresholds to von Frey filaments in the face (A) and hindpaw (B) regions of rats on D6 compared to baseline values. Co-infusion of CYM51317 (5 mg/kg/day) with sumatriptan prevented the development of triptan-induced sensitization on D6 in both the face and hindpaw regions. Exposure to saline co-infused with CYM51317 or vehicle did not produce any significant reductions in thresholds.

Reversal of bright light stress-induced allodynia with acute zyklophin

On D20 after pump implantation, sensory threshold levels for all groups had returned to pre-implantation baseline levels for both the periorbital (8±0.0g) and hindpaw (15±0.0g) regions. On D20 and D21, rats were exposed to BLS for 1 hour. On D21, rats were administered an injection of zyklophin (3 nmol, ICV) or saline 2 hours after the termination of the BLS when allodynia had already developed. ICV zyklophin reversed bright light stress-induced allodynia in sumatriptan pre-treated rats, with the greatest effect occurring 15 minutes post-injection (periorbital: $F_{(1,47)}$=27.298; p<.001; hindpaw: $F_{(1,47)}$=34.21; p<.001). Withdrawal thresholds dropped to 4.9±0.46g and 8.13±0.95g for the periorbital and hindpaw regions, respectively, 2 hours after the termination of the BLS. Fifteen minutes after ICV zyklophin, thresholds were elevated to 8±0.0g in the periorbital region and 14.06±0.76g in the hindpaw (Fig 3). No effect was observed with saline injection. ICV zyklophin had no effect on the tactile threshold in saline pre-exposed rats.

Reversal of bright light stress-induced allodynia with acute CYM51317

Rats were exposed to BLS on D20 and D21 for 1 hour. Acute administration of CYM51317 (20 mg/kg, p.o.) given at 2 hours post-BLS revered facial ($F_{(1,59)}$=7.58; p<.008) and hindpaw allodynia in sumatriptan pre-exposed rats, with the greatest effect occurring 30 minutes post-injection. Withdrawal thresholds elevated from 5.77±0.76g to 8±0.0g in the periorbital region and 7.46±1.07g to 13.82±1.18g in the hindpaw region 30 minutes after administration of CYM51317 (Fig 4). No effect was observed with saline administration.

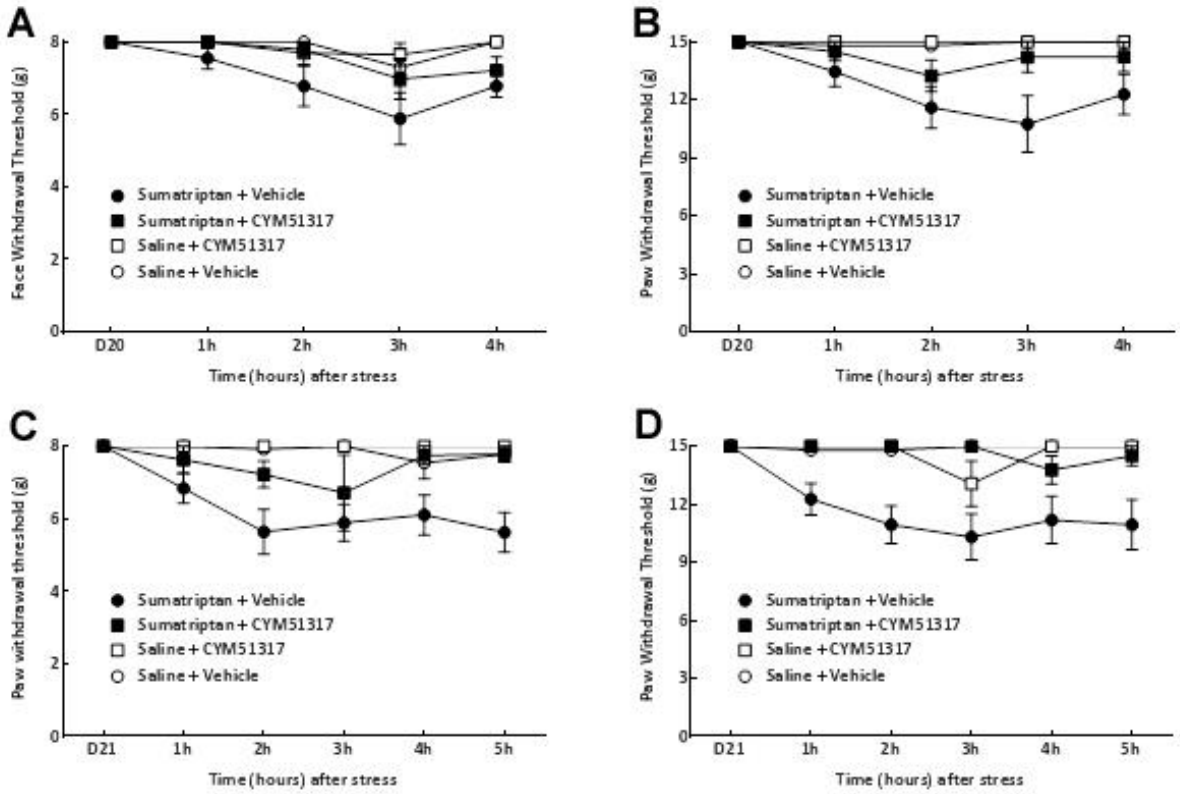

Figure 2: On D20 rats were exposed to bright light for 1 hour, which caused mild reductions in face (A) and hindpaw (B) withdrawal thresholds to von Frey filaments in rats exposed to sumatriptan co-infused with CYM51317 or vehicle. On D21, a second exposure to bright light produced a greater reduction in face (C) and hindpaw (D) thresholds in rats with sumatriptan/vehicle co-infusion. This enhanced allodynia on the second day of bright light exposure was blocked in rats co-infused with sumatriptan and CYM51317. Two-factor ANOVA indicates significant ($p<0.05$) differences between face and hindpaw thresholds between the sumatriptan/vehicle co-infusion and sumatriptan/CYM51317 co-infusion groups.

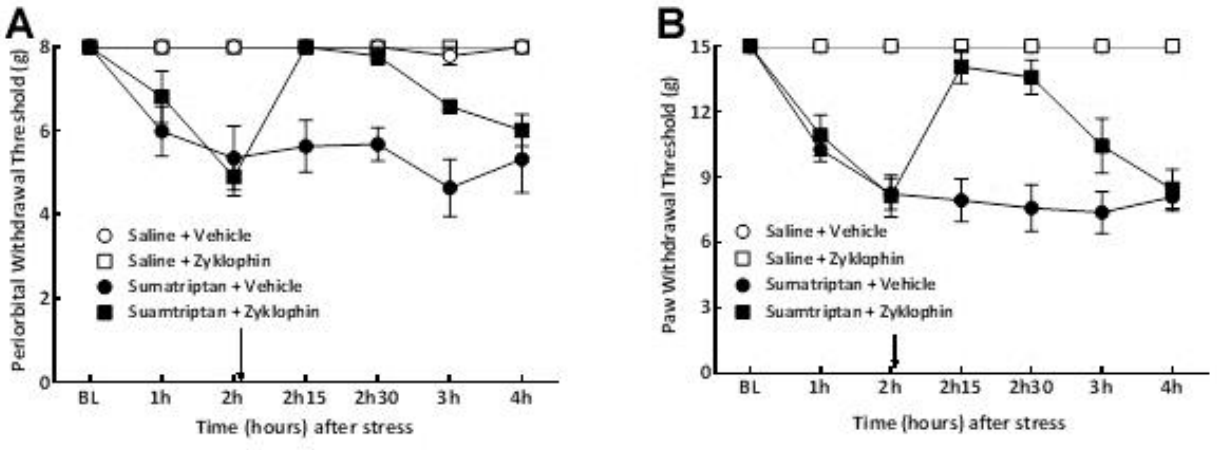

Figure 3: On D20 after pump implantation, rats were exposed to bright light for 1 hour. On D21, rats were exposed to bright light for 1 hour for a second time, then were administered zyklophin (3 nmol, ICV) two hours after the termination of the bright light. Groups that had been pretreated with sumatriptan showed significant reductions in withdrawal thresholds to von Frey filaments. Administration of zyklophin produced significant ($p<0.05$) reversal of stress-induced allodynia in the periorbital (A) and hindpaw (B) regions in rats pretreated with sumatriptan.

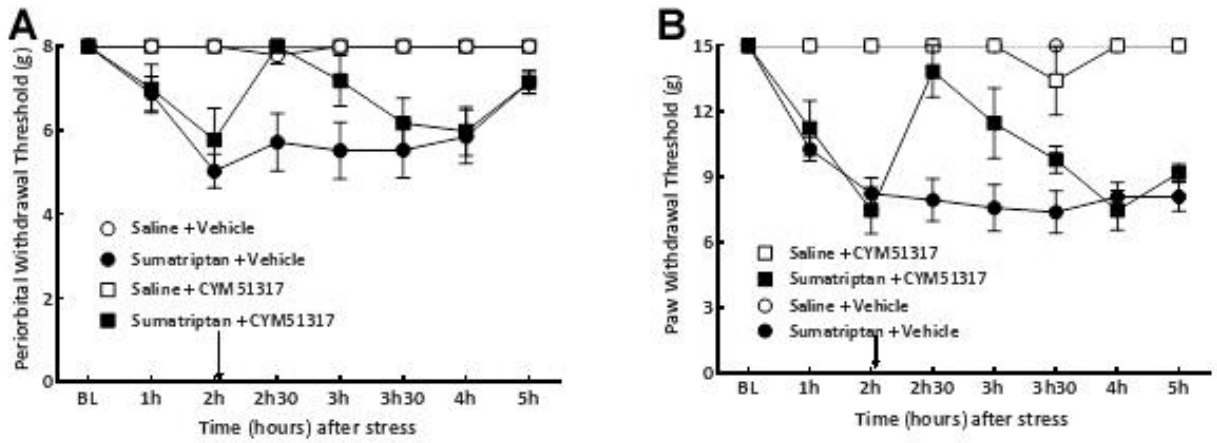

Figure 4: On D20 after pump implantation, rats were exposed to bright light for 1 hour. On D21, rats were exposed to bright light for 1 hour for a second time, producing significant reductions in withdrawal thresholds in sumatriptan pretreated rats. Administration of CYM51317 (20 mg/kg, p.o.) two hours after the termination of the bright light produced significant ($p<0.05$) reversal of stress-induced allodynia in the periorbital (A) and hindpaw (B) regions in sumatriptan pretreated rats.

Discussion

There is a high unmet clinical need for prophylactic migraine treatments, as many currently available options often take many weeks to take effect, can have significant side effects that limit their use, and patients may have decreased responsiveness to treatment over time. We demonstrated, for the first time, that KOR antagonists effectively relieve cephalic pain induced by bright light stress in a rat model of MOH. Thus, KOR seems to be a valid target for developing abortive or prophylactic medications for the treatment of migraine.

We used a well-characterized preclinical model of triptan-induced sensitization in rats that mimics the clinical symptoms associated with MOH in humans.[14] Migraine pain in humans occurs without injury to tissue. By using this model we were able to reliably induce cephalic pain without causing any damage to tissue (other than the implantation of mini-pumps), thus more closely exhibiting clinical observations in humans. A key feature of MOH is a lowered threshold for head pain[10] and to stressful triggers but normal sensory thresholds between migraine attacks. Stress is a highly reported trigger for migraine, and one study that followed patients for 6 months reported that stress was more likely to be found on the day before and the first day of a migraine attack.[17] It is important to note that we used an environmental stress in the form of bright light exposure, which has been shown to reliably induce enhanced sensory responsiveness in sensitized animals.[26] But it is possible that the effects of environmental stress may differ mechanistically from psychosocial stressors that may also trigger migraine.

We observed that systemic co-infusion of CYM51317 with sumatriptan prevented the development of sumatriptan-induced sensitization that was seen in controls after 6 days. Additionally, co-infusion of CYM51317 with sumatriptan reduced the effects of the bright light stressor on days 20 and 21 after pump implantation, which suggests that the stress response was attenuated by the KOR antagonist. We did not observe reductions in sensory thresholds with CYM51317/saline co-infusions, suggesting that the long-term use of this KOR antagonist did not cause the development of MOH-like symptoms as does sumatriptan, supporting the possible use as a replacement for currently available prophylactic treatments. These observations support our hypothesis that the use of a KOR antagonist may be effective as a prophylactic therapy for stress-induced migraine pain.

We tested two KOR antagonists, CYM51317 and zyklophin, as acute treatments after stress-induced allodynia had already been well developed on the second day of BLS exposure.

CYM51317 was administered orally, while zyklophin was injected into the ICV. Both compounds produced reversal of stress-induced allodynia, with effects occurring within 30 minutes after administration. Our observations show that KOR antagonists are not only effective as prophylactic treatments but may be used as abortive treatments after the onset of migraine pain as well.

Stress leads to a range of hormonal, autonomic, and behavioral changes.[28] In response to stress CRF is released from the hypothalamus, which has a stimulatory effect on the release of glucocorticoids and activation of the HPA axis. CRF is implicated in coordinating and the physiological stress response, including the release of dynorphin.[3,18] CRF and dynorphin are co-localized in the hypothalamus.[7] Stress exposure and ICV injection of CRF have been shown to cause increases in dynorphin levels[2,18] and subsequent KOR phosphorylation.[8] Dynorphin and KOR activity has been implicated in having a stimulatory effect on HPA axis activity.[7] Increased HPA activity promotes autonomic responses which can contribute to neurogenic inflammation in the meninges, which may be associated with the development and cephalic pain of migraine attacks. Activation of the dynorphin/KOR pathway has also been associated with enhanced release of CRF[7] and increased corticosterone levels in rats and cortisol levels in humans.[28] KOR-induced release of CRF may be evidence of a positive feedback loop that increases HPA activity, therefore enhancing the stress response. Previous studies done with rats have shown that disruption of KOR function may reduce HPA axis activity. Corticosterone levels were reduced in prodynorphin knockout rats and rats treated with a KOR antagonist,[28] further supporting a link between KOR and HPA activity. The correlations between KOR and HPA activity provide a basis for targeting the dynorphin/KOR system as a mechanism for pharmacological intervention to reduce the effects of stress, in this case migraine pain.

KORs have been found in elevated concentrations in rodent brain regions involved in the stress response and the endocrine actions of opioids, such as the paraventricular nucleus (PVN) of the hypothalamus, and amygdala, and a similar expression profile exists in the human brain.[7,28] Additionally, KORs are expressed at several levels of pain circuitry including the dorsal root ganglia, dorsal spinal cord, rostral ventromedial medulla (RVM), periaqueductal gray (PAG), and the sensory thalamus.[29] The PAG and lower brain stem may be supraspinal sites where KORs may have their effect nociception.[22] Descending pain inhibitory cells from the RVM are inhibited by the activation of KORs, which favors enhanced responsiveness to

activation of nociceptive trigeminal afferents. KOR activation has also been shown to activate MAPK pathways in neurons and astrocytes, thus KOR-mediated effects on ion channels and signaling cascades allow for rapid effects on cell excitability and neurotransmitter release that may underlie acute stress effects (19). It should be noted that CYM51317 was able to have effect when given systemically and orally, meaning this compound was able to cross the blood-brain barrier. Being able to cross the blood-brain barrier is very advantageous, allowing for easy and non-invasive administration. CYM51317 produced its effect within 30 minutes after oral administration, showing that the KOR system can be rapidly modulated by KOR antagonists.

The interpretation of the results we present here is consistent with the previous animal studies that have shown treatment with KOR antagonists blocks or reduces the effects of stress. Key aspects of KOR-mediated behaviors resemble those observed following stress of CRF administration, suggesting common mechanisms of action. The dynorphin/KOR system has been found to regulate neuronal excitability to affect learning, cognition, nociception, and endocrine function,[2] all of which can be heavily impacted by stress. Dynorphin/KOR activity is suggested be downstream from CRF release in stress-activated pathways. KOR antagonists have been shown to block aversive effects of CRF after injection or stress. Pretreatment with a KOR antagonist blocked CRF-induced conditioned-placed aversion (CPA)[18] as well as stress-induced CPA in rats.[8] In paradigms using forced swim or social defeat, stress-induced behavioral changes were blocked by administration of a KOR antagonist and absent in prodynorphin knockout mice.[2] Prodynorphin knockout mice and mice pretreated with a KOR antagonist displayed less time in defeat postures compared to controls in the social defeat stress paradigm.[2] This may imply that the dynorphin/KOR system not only affects the physiological portion of the stress response, but the psychological aspect as well. Additionally, activity of the dynorphin/KOR system may be specific to stress-responsive mechanisms and behaviors. One study reported that pretreatment of zyklophin prevented stress-induced reinstatement of cocaine-seeking behavior in a CPP test, but did not block cocaine-induced reinstatement.[8]

Our data suggest that blockade of the dynorphin/KOR system with selective antagonists reduces stress-induced migraine-like cephalic pain in rats. We tested our KOR antagonists as both abortive and prophylactic treatments by using a preclinical model that has features that are consistent with clinical observations of MOH, allowing us to draw conclusions that may be clinically relevant to migraine studies in humans. The dynorphin/KOR system is heavily

implicated as a critical mediator of the stress response for both rats and humans, making it a fitting target for pharmacological intervention in stress-related disorders. KOR antagonists are in the very early stages of preclinical study for use in migraine pain, but may offer options for both acute and prophylactic treatment of stress-induced migraine without the likelihood of causing the development of MOH.

References

1. Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB: Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. Headache 48:1157–68, 2008.

2. Bruchas MR, Land BB, Chavkin C: The dynorphin/kappa opioid system as a modulator of stress-induced and pro-addictive behaviors. Brain Res 1314:44–55, 2010.

3. Bruchas MR, Land BB, Lemos JC, Chavkin C: CRF1-R activation of the dynorphin/kappa opioid system in the mouse basolateral amygdala mediates anxiety-like behavior. PLoS One 4:e8528, 2009.

4. Burstein R, Collins B, Jakubowski M: Defeating migraine pain with triptans: a race against the development of cutaneous allodynia. Ann Neurol 55:19–26, 2004.

5. Burstein R, Jakubowski M: Analgesic triptan action in an animal model of intracranial pain: a race against the development of central sensitization. Ann Neurol 55:27–36, 2004.

6. Burstein R, Yarnitsky D, Goor-Aryeh I, Ransil BJ, Bajwa ZH: An association between migraine and cutaneous allodynia. Ann Neurol 47:614–24, 2000.

7. Calogero AE, Scaccianoce S, Burrello N, Nicolai R, Muscolo LA, Kling MA, Angelucci L, D'Agata R: The kappa-opioid receptor agonist MR-2034 stimulates the rat hypothalamic-pituitary-adrenal axis: studies in vivo and in vitro. J Neuroendocrinol 8:579–85, 1996.

8. Carroll FI, Carlezon W a: Development of κ opioid receptor antagonists. J Med Chem 56:2178–95, 2013.

9. Dixon WJ: Efficient analysis of experimental observations. Annu Rev Pharmacol Toxicol 20:441–62, 1980.

10. Dodick D, Freitag F: Evidence-based understanding of medication-overuse headache: clinical implications. Headache 46 Suppl 4:S202–11, 2006.

11. Dodick D, Silberstein S: Central sensitization theory of migraine: clinical implications. Headache 46 Suppl 4:S182–91, 2006.

12. De Felice M, Eyde N, Dodick D, Dussor GO, Ossipov MH, Fields HL, Porreca F: Capturing the aversive state of cephalic pain preclinically. Ann Neurol:257–65, 2013.

13. De Felice M, Ossipov MH, Porreca F: Persistent medication-induced neural adaptations, descending facilitation, and medication overuse headache. Curr Opin Neurol 24:193–6, 2011.

14. De Felice M, Ossipov MH, Wang R, Lai J, Chichorro J, Meng I, Dodick DW, Vanderah TW, Dussor G, Porreca F: Triptan-induced latent sensitization: a possible basis for medication overuse headache. Ann Neurol 67:325–37, 2010.

15. Ghiotto N, Sances G, Galli F, Tassorelli C, Guaschino E, Sandrini G, Nappi G: Medication overuse headache and applicability of the ICHD-II diagnostic criteria: 1-year follow-up study (CARE I protocol). Cephalalgia 29:233–43, 2009.

16. Jamensky NT, Gianoulakis C: Content of dynorphins and kappa-opioid receptors in distinct brain regions of C57BL/6 and DBA/2 mice. Alcohol Clin Exp Res 21:1455–64, 1997.

17. Kelman L: The triggers or precipitants of the acute migraine attack. Cephalalgia 27:394–402, 2007.

18. Land BB, Bruchas MR, Lemos JC, Xu M, Melief EJ, Chavkin C: The dysphoric component of stress is encoded by activation of the dynorphin kappa-opioid system. J Neurosci 28:407–14, 2008.

19. Landy S, Rice K, Lobo B: Central sensitisation and cutaneous allodynia in migraine: implications for treatment. CNS Drugs 18:337–42, 2004.

20. Maleki N, Becerra L, Borsook D: Migraine: maladaptive brain responses to stress. Headache 52 Suppl 2:102–6, 2012.

21. Meng ID, Dodick D, Ossipov MH, Porreca F: Pathophysiology of medication overuse headache: insights and hypotheses from preclinical studies. Cephalalgia 31:851–60, 2011.

22. Minami M, Hosoi Y, Toya T, Katao Y, Maekawa K, Katsumata S, Yabuuchi K, Onogi T, Satoh M: In situ hybridization study of κ-opioid receptor mRNA in the rat brain. Neurosci Lett 162:161–4, 1993.

23. Noseda R, Burstein R: Migraine pathophysiology: anatomy of the trigeminovascular pathway and associated neurological symptoms, cortical spreading depression, sensitization, and modulation of pain. Pain 154 Suppl :S44–53, 2013.

24. Olesen J, Bousser M-G, Diener H-C, Dodick D, First M, Goadsby PJ, Göbel H, Lainez MJ a, Lance JW, Lipton RB, Nappi G, Sakai F, Schoenen J, Silberstein SD, Steiner TJ: New appendix criteria open for a broader concept of chronic migraine. Cephalalgia 26:742–6, 2006.

25. Olesen J, Burstein R, Ashina M, Tfelt-Hansen P: Origin of pain in migraine: evidence for peripheral sensitisation. Lancet Neurol 8:679–90, 2009.

26. Rivat C, Laboureyras E, Laulin J-P, Le Roy C, Richebé P, Simonnet G: Non-nociceptive environmental stress induces hyperalgesia, not analgesia, in pain and opioid-experienced rats. Neuropsychopharmacology 32:2217–28, 2007.

27. Silberstein S: Migraine. Lancet 363:1399, 2004.

28. Van't Veer A, Carlezon W a: Role of kappa-opioid receptors in stress and anxiety-related behavior. Psychopharmacology (Berl) 229:435–52, 2013.

29. Wang Y, Sun J, Tao Y, Chi Z, Liu J: The role of kappa-opioid receptor activation in mediating antinociception and addiction. Acta Pharmacol Sin 31:1065–70, 2010.