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Capturing the aversive state of cephalic pain preclinically

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Abstract

Objective—Preclinical evaluation of headache by behavioral assessment of reward from pain relief.

Methods—Inflammatory mediators (IM) or control solutions were applied to the rat dura mater to elicit a presumed state of cephalic pain. Hindpaw incision was used in separate groups of animals to model non- cephalic post-surgical pain. Drugs were given systemically or microinjected within the rostral ventromedial medulla (RVM), nucleus accumbens (NAc) or rostral anterior cingulate cortex (rACC). Peripheral nerve block (PNB) was produced at the level of the popliteal fossa and behavior was assessed using evoked sensory stimuli or conditioned place preference (CPP). Immunohistochemistry and brain microdialysis measurements were performed.

Results—Dural IM produced long-lasting generalized cutaneous allodynia (CA). RVM lidocaine produced CPP, increased NAc c-FOS and dopamine (DA) release selectively in rats receiving dural IM; CPP was blocked by intra-NAc α -flupenthixol, a dopaminergic antagonist. Intravenous α CGRP₍₈₋₃₇₎ produced CPP and elicited NAc dopamine release selectively in rats with dural IM. Prior lesion of the rACC or treatment with systemic sumatriptan, or α CGRP₍₈₋₃₇₎ abolished RVM lidocaine-induced CPP in IM-treated rats. Sumatriptan treatment blocked NAc dopamine release in IM treated rats receiving RVM lidocaine. Systemic sumatriptan did not alter pain-relief induced CPP in rats with incisional injury.

Interpretation—Cephalic pain was unmasked in rats by assessment of motivated behavior to seek relief. Relief of pain activates the dopaminergic reward pathway to elicit negative reinforcement of behavior. Medications clinically effective for migraine headache selectively elicit relief of ongoing cephalic, but not post-surgical, non-cephalic pain. These studies provide a platform for exploring migraine pathophysiology and for the discovery of new headache therapies.

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Introduction

Mechanisms of migraine, and other primary headache disorders, are not well understood, current treatments are often inadequate, and therapeutic advances have been remarkably slow with only one class of medication (triptans) specific for migraine developed and approved over the past half-century. A principle barrier to novel drug discovery for migraine is the relative lack of predictive preclinical models of headache.

In humans, headache pain is thought to result from activation of nociceptors that innervate the dura mater¹. We reported that application of inflammatory mediators (IM) onto the rat dura mater activates afferent fibers from this tissue, elicits a delayed and generalized state of cutaneous allodynia (CA) and increases firing of pain facilitatory “ON”-cells of the rostral ventromedial medulla (RVM)². Subsequent inactivation of the RVM with local anesthetic blocks IM-induced CA². While CA likely represents a state of nociceptor-driven central sensitization that may be relevant to clinical observations³, it is not a direct measure of ongoing pain that might reflect potential headache.

Pain is unpleasant⁴ and provides strong motivational drive to seek relief. We have captured this motivated behavior in rats using conditioned place preference (CPP)^{5–8} to pain relieving treatments, i.e., negative reinforcement. The aversive state reflecting ongoing or spontaneous inflammatory, incisional, neuropathic or osteoarthritic pains were “unmasked” using this approach^{5–8}. Importantly, lesions of the rostral anterior cingulate cortex (rACC) blocked CPP resulting from pain relief, but not from positively reinforcing drugs (e.g., cocaine)^{8, 9}. Relief of pain is rewarding in humans¹⁰ and in rats¹². We have recently demonstrated that peripheral nerve block (PNB)-induced relief of ongoing post-surgical pain in rats results in activation of mesolimbic dopaminergic reward circuits¹¹.

We hypothesized that directly activating rat trigeminal nociceptors would elicit cephalic pain, possibly serving as an animal model of “headache”. We determined if such pain could be captured by assessment of negative reinforcement, if selective relief of cephalic pain is produced by clinically effective headache medications and if such treatments activate the mesolimbic reward circuit. Additionally, we hypothesized that sumatriptan would fail to block non-cephalic post surgical pain, consistent with clinical experience with this drug.

Materials and methods

Animals

Male S.D. rats (250–350 g, Harlan) were used in accordance with NIH guidelines under protocols approved by the Institutional Animal Care and Use Committee. Rats were housed on a 12 h, light-dark cycle with food and water *ad libitum*. All behavioral experiments were performed by experimenters blinded to the treatment conditions.

Surgical Preparation

Dural cannulation and inflammation—The dura of anesthetized (ketamine/xylazine 80/12mg/kg, i.p.) rats was exposed through 2 burr holes (1mm) 6 mm apart and guide cannulae were placed extending 0.5 mm from the skull surface above the dura and secured

with dental acrylic^{2, 12}. Gentamycin (1 mg/kg) was given after surgery followed by a 7 day recovery. Infusions (10 μ L/cannula) of inflammatory mediator (IM) or synthetic interstitial fluid (SIF) were made over 30 sec in each cannula.

Intracranial RVM and NAc Cannulation—Pairs of guide cannulae were directed towards the RVM or NAc shell of anesthetized rats for drug microinjections. A single guide cannula for microdialysis (AG-8, EICOM Corp., Kyoto, Japan) was implanted into the left NAc. Gentamycin (1 mg/kg) was given after surgery followed by a 7 day recovery.

Rostral anterior cingulate cortex (rACC) lesions—Anesthetized rats received microinjection of ibotenic acid (0.5 μ g/0.6 μ L) in 0.1 M phosphate-buffered saline (PBS; pH 7.4) or 0.1M PBS (sham lesions) into the rACC in each hemisphere as previously described^{8, 13}. Lesions were confirmed post-hoc histologically.

Incisional injury—Incision injury of the hindpaw skin plus deep tissue, including fascia and underlying muscle was performed as previously described¹⁴.

Drug administration

Brain microinjection—Bilateral microinjections (0.5 μ L) of 4% lidocaine HCl (RVM) or 3 μ g α -flupenthixol (NAc) (Sigma, St. Louis, MO) were made through injectors extending 1 mm beyond the guide cannula. Cannula placement was subsequently confirmed histologically. Data from animals with misplaced cannulas (“off-site”) were analyzed separately (Supplemental Fig. 1).

Systemic treatments—Sumatriptan (NeurAxon, Toronto, Canada) and α -CGRP₈₋₃₇ (Bachem, King of Prussia, PA) were dissolved in saline and given at doses and time as previously reported^{12, 15, 16}.

Peripheral nerve block—Saline or lidocaine (200 μ L; 4%; Qualitest, Huntsville, AL) was injected into popliteal fossa (PF) under light isoflurane anesthesia as previously described¹¹.

Behavioral Testing

Evoked hypersensitivity—Somatosensory thresholds to tactile stimuli were determined by application of von Frey filaments to the periorbital or hindpaw regions until a withdrawal response was elicited^{12, 15, 16}. The 50% withdrawal thresholds were determined by the Dixon up-down method¹⁷.

Conditioned Place Preference (CPP) Procedures—Rats were handled for 2 days prior to preconditioning. On preconditioning day, rats had free access to CPP boxes consisting of two compartments with distinct visual, tactile and odor cues that were separated by a third middle neutral chamber. Time spent in each chamber was electronically recorded^{5, 6}. On conditioning day, rats received RVM saline and were immediately placed into one “pairing” chamber for 30 minutes. Rats then received dural SIF or IM injections. After 3 hours, they received either RVM lidocaine or saline and were placed in the opposite

chamber in a counterbalanced design. After 20 hours (test day), the rats had free access to all chambers for 15 minutes and the time spent in each chamber was recorded. Difference scores were calculated as the difference between the baseline and post-conditioning times spent in the lidocaine-paired chamber.

For the post-surgical pain study, different groups of animals, on preconditioning day after baseline underwent hindpaw incision. On conditioning day, rats received RVM or PF saline and were immediately placed into one “pairing” chamber for 30 minutes. After 4 hours (24h post incision), they received RVM or PF lidocaine and were placed in the opposite chamber in a counter-balanced design. On test day, rats had free access to all chambers for 15 minutes.

Immunohistochemistry

Two hours after RVM treatment, rats were anesthetized and transcardially perfused with 4% paraformaldehyde and FOS immunohistochemistry performed (Supplemental Methods).

In vivo microdialysis and HPLC quantification of dopamine

Microdialysis probes were inserted into the NAc of awake, freely moving animals and dopamine release was measured (Supplemental methods). Dopamine concentrations were expressed as % of the corresponding baseline level and differences in the area under the curve (AUC).

Statistical Analysis

Results were expressed as mean $\pm$ SEM. CPP data were analyzed using paired t-test (pre-conditioning vs post-conditioning). One-way ANOVA was used for comparison among groups. Significance was set at $p \leq 0.05$. Two-factor ANOVA was used to detect differences between treatment groups over time.

Results

Dural IM-induced periorbital and hindpaw allodynia and ongoing pain

IM delivered by two previously implanted cannulae produced a delayed and significant ($F_{(1,115)} = 52.38$, $p = 5.52 \times 10^{-11}$ and $F_{(1,115)} = 24.7$, $p = 2.32 \times 10^{-6}$ for hindpaw and periorbital, respectively) cutaneous allodynia (CA) that was detected for up to 24h (Fig 1A). Dural application of synthetic interstitial fluid (SIF) did not alter sensory thresholds (Fig 1A).

No pre-conditioning differences were observed among the treatments groups, allowing the pooling of the pre-conditioning baseline values (BL) for graphical representation (Fig 1C). Lidocaine microinjected into the RVM produced chamber preference only in rats with dural inflammation, indicated by a significant difference score ($t_{(88)} = -6.88$, $p = 4.09 \times 10^{-10}$) (Fig. 1D). Rats that received saline injection into the RVM during both conditioning sessions did not show CPP (data not shown). RVM lidocaine in SIF treated rats did not elicit CPP (Fig 1D, $t_{(23)} = -0.78$, $p = 0.22$). CPP was not produced in rats with “off-site” lidocaine microinjections (Fig 1D, $t_{(21)} = 0.04$, $p = 0.48$, Supplemental Fig. 1).

Intravenous α CGRP₍₈₋₃₇₎ (0.45 mg/kg) injected three hours post dural SIF or IM produced CPP selectively in IM-treated rats. α CGRP₍₈₋₃₇₎ produced chamber preference indicated by a significant difference score ($t_{(11)} = -2.28$, $p = 0.02$) (Fig. 2B) in IM- but not in SIF-, treated rats (Fig 2B, $t_{(9)} = 0.94$, $p = 0.18$).

Intravenous sumatriptan (0.3 or 1.2 mg/kg) injected three hours post dural SIF or IM did not produce CPP as indicated by a non-significant difference score ($t_{(8)} = 0.25$, $p = 0.41$, $t_{(9)} = 0.37$, $p = 0.36$, respectively) in IM- or SIF-, treated rats (Supplemental Fig 2B, $t_{(9)} = 0.18$, $p = 0.43$, $t_{(9)} = 0.83$, $p = 0.21$, respectively).

rACC lesion blocks RVM lidocaine-induced CPP

IM-induced CA was not altered in rats with rACC lesion^{8, 13}; no differences in periorbital ($F_{(1,48)} = 0.05$, $p = 0.82$) or hindpaw ($F_{(1,48)} = 0.27$, $p = 0.61$) response thresholds were detected between the sham-operated and lesioned groups (Fig 3A). Rats with sham rACC lesion and with dural IM showed a significant ($t_{(12)} = -2.69$, $p = 0.01$) CPP to RVM lidocaine (Fig 3B). In contrast, RVM lidocaine did not produce CPP in rats with rACC lesions and dural IM (Fig 3B, $t_{(20)} = -1.15$, $p = 0.13$).

Pharmacological blockade of RVM lidocaine-induced CPP

As sumatriptan and CGRP antagonists are clinically effective against migraine pain¹⁸⁻²⁰, rats received sumatriptan (0.6 mg/kg, s.c.) or α CGRP₍₈₋₃₇₎ (0.45 mg/kg, i.v.) 30 min post-IM or SIF, as previously described^{12, 15, 16}, followed 2.5h later by RVM lidocaine or saline for assessment of CPP. Both sumatriptan and α CGRP₍₈₋₃₇₎ prevented CPP to RVM lidocaine in rats with dural IM, as indicated by non-significant difference scores ($t_{(14)} = 0.69$, $p = 0.25$; $t_{(9)} = 0.52$, $p = 0.31$ respectively)(Fig. 4B). In contrast, CPP to RVM lidocaine in rats with dural IM was present in rats receiving s.c. or i.v. saline, as shown by significant ($t_{(9)} = -2.07$, $p = 0.03$; $t_{(8)} = -2.23$, $p = 0.03$ respectively) difference scores. Administration of these drugs to SIF-treated rats did not produce CPP or conditioned place aversion (data not shown).

RVM lidocaine activates mesolimbic dopaminergic circuit in IM-treated rats

Microinjection of RVM lidocaine 3h after dural IM produced a significant ($F_{(3,130)} = 10.37$; $p = 0.36 \times 10^{-5}$) increase to 10.8 ± 0.6 c-Fos positive profiles/section in the NAc shell in IM-treated rats relative to rats with dural SIF and RVM lidocaine (5.8 ± 0.9 profiles/section) (Fig. 5A). Dural IM or SIF alone resulted in 6.7 ± 0.8 and 6.6 ± 0.7 c-Fos positive profiles/section, respectively, which were not significantly different from those of the RVM lidocaine/SIF group (Fig. 5A).

Dural SIF or IM did not significantly alter baseline NAc dopamine levels prior to RVM lidocaine. Dopamine levels were 3.6 ± 0.8 pg/30 FL and 2.5 ± 0.4 pg/30 μ L, in SIF and IM treated rats, respectively. There were no significant changes in NAc dopamine levels in the SIF-treated groups or the IM-treated group receiving RVM saline (Fig. 5B). In contrast, rats with IM receiving RVM lidocaine showed a significant increase in NAc dopamine compared to baseline values. The area under the time-effect curve (AUC) (AUC = 4438.53

± 1460.34) was significantly ($F_{(3,25)}=4.29$; $p = 0.01$) greater than that of the SIF/RVM saline treated group (Fig. 5B).

Intravenous α CGRP₍₈₋₃₇₎ (0.45 mg/kg) injected 3hr post dural IM produced a significant increase in NAc dopamine release compared to baseline values. The AUC (5501.29 ± 1883.29) was significantly ($F_{(3,20)}=4.22$; $p = 0.02$) greater than that of the SIF/i.v. saline treated group (Fig. 5C). α CGRP₍₈₋₃₇₎ (0.45 mg/kg, i.v.) did not change dopamine release in SIF treated rats (Fig. 5C).

Pretreatment with systemic sumatriptan (0.6 mg/kg, s.c., 30 min post dura injection) significantly blocked NAc dopamine release in rats with IM and RVM lidocaine (AUC value of 1109.23 ± 1359.79) (Fig 5D). Sumatriptan did not affect NAc dopamine release in SIF or IM treated rats, following RVM saline or lidocaine injection ($F_{(3,16)}=0.83$; $p = 0.50$) (Fig 5D). Additionally, s.c. sumatriptan given 2.5 hr prior to RVM microinjection, did not increase dopamine release relative to pre dura-stimulation levels ($F_{(1,20)}=0.26$; $p = 0.61$) (Supplemental Fig. 2).

Pretreatment with α -flupenthixol (3 μ g) microinjected into the NAc 10 min prior to RVM lidocaine prevented CPP in rats with dural inflammation, as indicated by a non-significant difference score ($t_{(13)} = -0.39$, $p = 0.35$) (Fig. 5E). In contrast, saline microinjected into the NAc did not block CPP, indicated by a significantly ($t_{(11)} = -2.20$, $p = 0.02$) increased difference score (Fig. 5E).

Systemic sumatriptan does not block non-cephalic ongoing pain

In rats with hindpaw incision, sumatriptan (0.6 mg/kg, s.c.) or saline was given 2.5h prior to RVM (Fig. 6B) or PF lidocaine-induced CPP (Fig. 6C) and CPP assessed. Sumatriptan pretreatment failed to prevent RVM lidocaine-induced CPP or PNB-induced CPP in rats with incisional pain, as indicated by a significant difference score ($t_{(12)} = -1.96$, $p=0.04$ for RVM lidocaine and $t_{(21)} = -1.81$, $p = 0.04$ for PNB) (Fig. 6B,C). In contrast, RVM or PF saline did not block CPP, indicated by a significantly ($t_{(8)} = -1.83$, $p = 0.05$, $t_{(20)} = -1.76$, $p = 0.05$, respectively) increased difference score (Fig. 6B,C).

Discussion

The unpleasantness of pain⁴ provides strong motivational drive²¹ to seek relief. Relief of pain is rewarding in humans¹⁰ and in animals¹¹. We previously demonstrated that pain relief-induced CPP can be used to reveal ongoing pain⁵⁻⁸. Here, we hypothesized that activation of dural nociceptors would produce an aversive state that might serve as an animal model of “headache” pain. This possibility was supported by multiple observations. First, RVM inactivation with lidocaine or administration of i.v. α CGRP₍₈₋₃₇₎ produced CPP selectively in animals with IM-induced dural inflammation. Second, presumed elimination of pain-induced aversiveness by lesion of the rACC, or by systemic administration of sumatriptan or α CGRP₍₈₋₃₇₎ prevented RVM lidocaine-induced CPP in IM-treated rats. Third, in rats with dural IM RVM lidocaine increased dopamine release in the NAc shell, an effect that was blocked by prior systemic sumatriptan. I.v. α CGRP₍₈₋₃₇₎ also increased NAc dopamine release selectively in rats with dural IM. Fourth, RVM lidocaine-induced CPP in

rats with dural IM was blocked by the non-selective dopaminergic antagonist, α -flupenthixol²², suggesting negative reinforcement from activation of NAc dopaminergic receptors. Fifth, consistent with the known selective clinical efficacy of triptans for headache pain, systemic sumatriptan failed to block CPP resulting from relief of hindpaw post-surgical pain with PNB or RVM lidocaine.

Migraine patients often demonstrate CA ipsilateral to headache pain that may also spread to the contralateral and extracephalic regions³. The development of CA is time-related and likely reflects nociceptor driven central sensitization^{3, 23}. Application of IM to the rat dura mater activates nociceptive afferents²⁴. We have previously demonstrated increased FOS expression in trigeminal nucleus caudalis and a time-related development of generalized CA in the facial and hindpaw regions likely reflecting central sensitization observed clinically¹². Additionally, we demonstrated that dural IM activates RVM pain facilitation (i.e., "ON") cells and that CA is blocked by local anesthetic RVM inactivation. These data support the hypothesis that dural IM activates primary afferent nociceptors that likely elicits cephalic pain and that such pain might be modulated by inactivation of the RVM.

RVM lidocaine produced CPP selectively in rats receiving dural IM, but not SIF, suggesting the presence of an aversive state likely reflecting ongoing headache pain. Importantly, off-site lidocaine injections failed to produce CPP in rats with dural IM. CPP represents learning to associate a context with a treatment that could elicit reward. Here, we measured CPP reflecting the reward of treatments that may relieve presumed cephalic pain. In this procedure, drug kinetics are important for potential learning. Thus, it is not clear when a systemically delivered drug might produce a change in pain state and this could result in a failure of the animals to associate a possible effect with the context. Thus, α CGRP₍₈₋₃₇₎ was given by the i.v. route resulting in CPP and NAc dopamine release selectively in animals with dural IM. Additionally, possible effects of systemic pretreatment with sumatriptan or α CGRP₍₈₋₃₇₎ on RVM lidocaine-induced CPP in IM treated rats was evaluated. If these treatments eliminate the pain-induced aversive state, then RVM lidocaine should no longer produce CPP. The lack of CPP observed following these pretreatments support the conclusion that sumatriptan or α CGRP₍₈₋₃₇₎ were effective in relieving IM-induced ongoing pain, consistent with clinical observation¹⁸⁻²⁰. 5HT_{1D} receptors have been shown to be present in nociceptors throughout the body²⁵, suggesting that triptans might also regulate nociceptive responses in extracranial tissues. Systemic sumatriptan has been suggested to block inflammatory- as well as non-inflammatory visceral pain, most likely through action at peripheral 5HT_{1B/D} receptor²⁶. In contrast, in the present study we show that systemic sumatriptan failed to abolish CPP in animals with post-surgical pain, consistent with selective clinical effectiveness for headache pain.

Human imaging data suggest that pain aversiveness is integrated, in part, within the rACC^{27, 28}. Cingulotomy has been reported to eliminate affective, but not sensory, dimensions of pain²⁹⁻³¹. In rats, activation of rACC glutamatergic receptors elicits conditioned place aversion (CPA) and rACC lesions eliminate CPA to hindpaw formalin without affecting evoked behaviors¹³. Additionally, rACC lesion eliminated CPP to RVM lidocaine in rats with experimental neuropathic pain⁸. Consistent with these reports in

humans and in animals, rACC lesion inhibited CPP to RVM lidocaine in IM treated rats without altering evoked responses suggesting modulation of aversiveness of headache pain.

Circuits underlying negative reinforcement have only recently begun to be explored. fMRI and PET imaging studies in humans demonstrate that pain offset produces activation of the NAc³² and that placebo response produces release of NAc dopamine³³. We have shown that rats with ongoing post-surgical pain showed both CPP and activation of the mesolimbic dopaminergic reward circuit after peripheral nerve block¹¹. Here, RVM lidocaine increased dopamine release and activation of NAc c-Fos selectively in animals with dural IM. Importantly, the increased NAc dopamine release produced by RVM lidocaine in IM-treated rats was blocked by sumatriptan supporting the conclusion that relief of cephalic pain is rewarding. Additionally, i.v., α CGRP₍₈₋₃₇₎ produced CPP and increased NAc dopamine. However, we did not detect increased NAc dopamine in IM-treated rats following systemic sumatriptan. While the reasons for this are not clear, it is possible that early treatment with sumatriptan (i.e. 30 min post IM injection) might prevent the development of, or significantly diminish the eventual intensity of headache pain so that changes in NAc dopamine could not be detected within the sensitivity limits of our measurements. Analytical methods with improved temporal resolution may allow possible changes to be detected in future studies. Importantly, NAc dopaminergic receptor blockade prevented CPP from RVM lidocaine in IM treated rats. These data suggest that activation of dopaminergic reward mechanisms underlie the negative reinforcement resulting from RVM lidocaine in IM treated rats, a conclusion supported by our previous studies with PNB in animals with post-surgical injury¹¹. Paradoxically, dopaminergic antagonists (e.g., haloperidol, droperidol) are effective in relieving migraine pain^{34, 35}. The mechanisms by which dopaminergic antagonists relieve migraine pain are unknown. However, systemic haloperidol increases dopamine release in the NAc shell³⁶, and dopamine antagonists increase dopaminergic cell firing possibly as a consequence of blockade of dopaminergic autoreceptors³⁷.

Our data suggest that activation of dural nociceptors produces an aversive state that can be captured by assessment of the motivational drive to seek a context paired with a pain relieving treatment, consistent with the presence of ongoing headache pain. Clinically relevant acute migraine-specific treatments demonstrated that relief of experimental cephalic pain results in activation of dopaminergic reward mechanisms. This approach may be employed to evaluate novel mechanisms with increased translational relevance for discovery of treatments for migraine and other primary headache disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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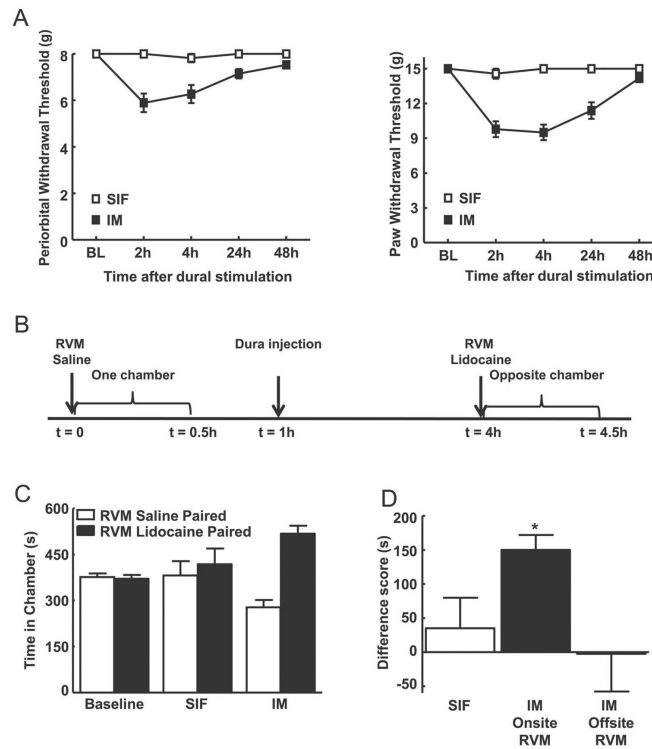


Figure 1.

Inactivation of descending modulation produces conditioned place preference only in rats treated with dural IM. A) Administration of IM (2 mM histamine, serotonin, bradykinin, and 0.2 mM PGE₂ in 10 mM Hepes buffer, pH 5.0) onto the dura, through 2 migraine guide cannulas (AP: bregma +1 mm; ML: midline +1.0 mm and AP: bregma -5 mm; ML: midline -1.0 mm) produced a robust and long-lasting periorbital as well as hindpaw allodynia (N=18). No allodynia was observed in SIF (10 mM Hepes, 5 mM KCl, 1 mM MgCl₂, 5 mM CaCl₂, and 135 mM NaCl, pH 7.3) treated rats (N=7). B) Protocol for evaluation of CPP. C) Microinjection of lidocaine (4% in 0.5 µl/site) into the RVM (AP: bregma -11mm; ML: ±0.6 mm; DV: skull -8.5 mm) induced CPP selectively in IM treated rats (N=89). No chamber preference was observed in SIF treated rats (N=24). D) Difference score calculated as test time – baseline time spent in the lidocaine paired chamber confirming that only IM treated rats with onsite RVM lidocaine injections showed CPP (p<0.05).

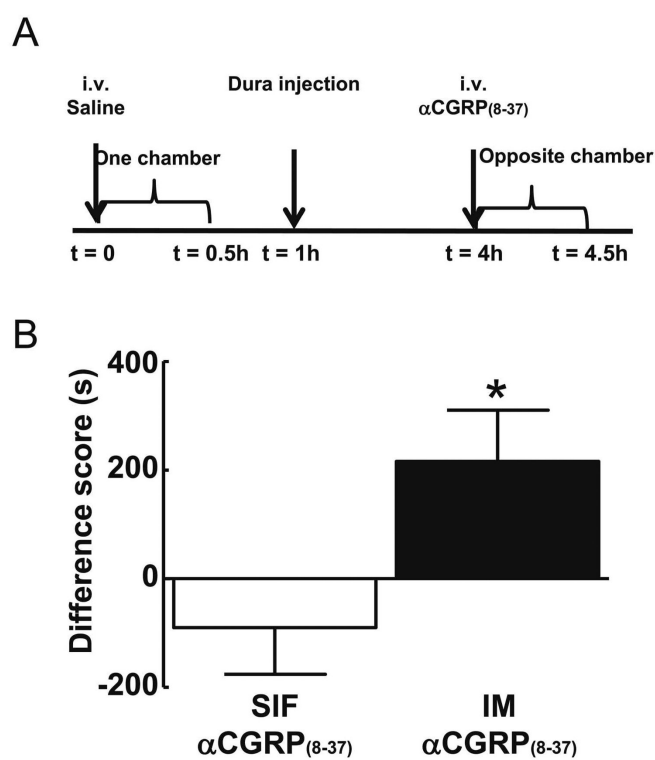


Figure 2. α CGRP₍₈₋₃₇₎ (0.45 mg/kg, i.v.) produces CPP in rats with dural IM. A) Protocol for injections on conditioning day. B) α CGRP₍₈₋₃₇₎ (0.45 mg/kg, i.v.) administered 3 hrs post dural injection induced CPP selectively in rats with IM (N=12); no significant differences were observed in rats treated with dural SIF (N=10).

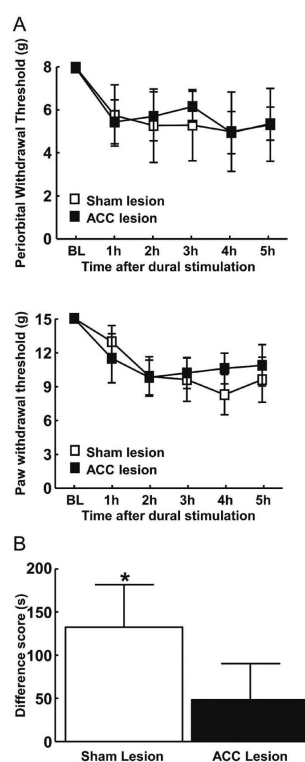


Figure 3. Lesion of the rACC (AP: +2.6 mm from bregma, DV 2.5 mm, ML $\pm$ 0.6 mm) blocks CPP resulting from RVM lidocaine in rats with dural IM. A) IM-induced allodynia was not prevented by lesion of the rACC. B) RVM lidocaine-induced CPP was blocked by ACC lesion.

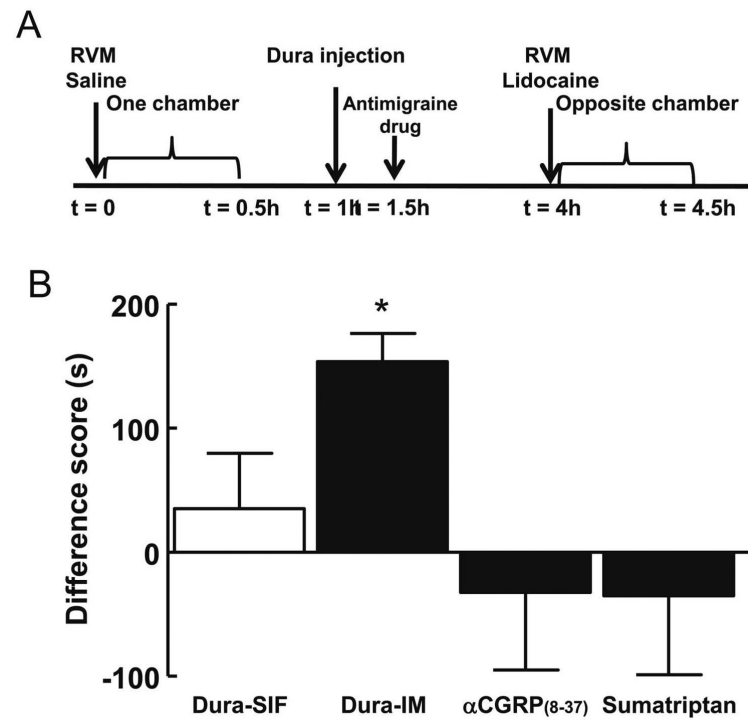


Figure 4. RVM lidocaine-induced CPP is blocked by clinically effective migraine treatments. A) Representation of time of injections for conditioning day. B) α CGRP₍₈₋₃₇₎ (0.45 mg/kg, i.v.) or sumatriptan (0.6 mg/kg, s.c.) administered 30 min post IM on the dura prevent RVM lidocaine-induced CPP.

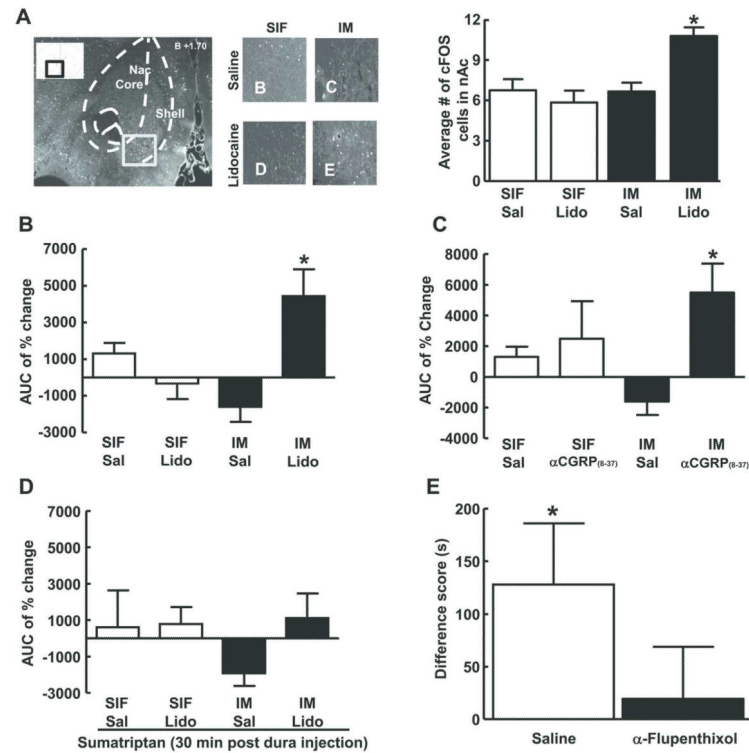


Figure 5.

Pain relief activates the mesolimbic dopaminergic reward pathway. A) RVM lidocaine selectively increases expression of cFOS in the NAc shell of rats with IM on the dura. B) RVM lidocaine elicited release of dopamine only in rats with dural IM. As a control for microdialysis procedures, rats received cocaine (20 mg/kg i.p.) at the end of the experiments to confirm evoked release of NAc dopamine. Rats that failed to respond to cocaine with increased dopamine efflux (<10%) were excluded from the analysis. No difference in DA release after cocaine was found between SIF and IM-treated rats. C) i.v. α CGRP₍₈₋₃₇₎ induced release of NAc dopamine only in rats with dural IM. I.v. α CGRP₍₈₋₃₇₎ administered 3h post IM induced DA release in the NAc shell of rats. No difference in DA release after cocaine was found in rats that received α CGRP₍₈₋₃₇₎. D) Systemic sumatriptan (0.6 mg/kg, s.c., 30 min post dura injection) blocked RVM lidocaine-induced NAc DA release in IM treated rats. No difference in DA release after cocaine was found in rats that received systemic sumatriptan. E) Inhibition of dopamine receptors in the NAc (AP: bregma +1.5 mm; ML: midline $\pm$ 1.0 mm; DV: skull -6.5 mm) prevented RVM lidocaine-induced CPP. On conditioning day rats received saline injection into the NAc (AP: bregma +1.5 mm; ML: midline $\pm$ 1.0 mm; DV: skull -6.5 mm) followed 10 min later by RVM saline and were immediately placed into the appropriate pairing chambers. Four hours later, rats received microinjections of α -flupenthixol (3 μ g/0.5 μ l/side) into the NAc followed within 10 min by RVM lidocaine injection and placement into the opposite chamber.

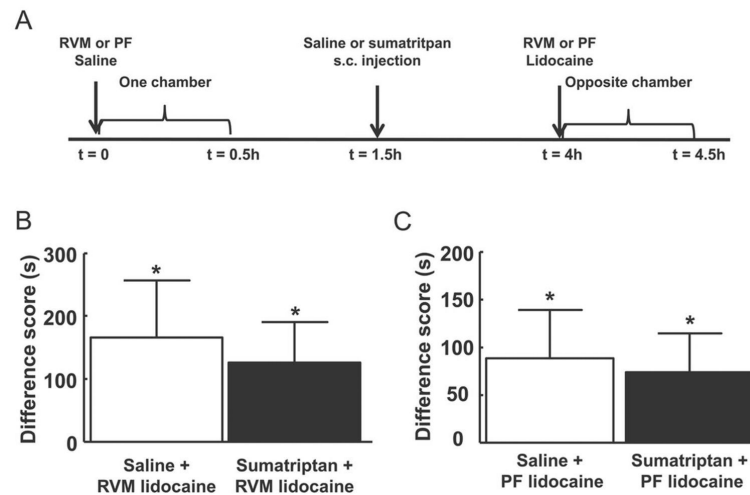


Figure 6.

Systemic sumatriptan does not prevent CPP in post-surgical pain. A) Protocol for injections for conditioning day. B) Sumatriptan (0.6 mg/kg, s.c.) administered 2.5h prior to RVM lidocaine did not prevent RVM lidocaine-induced CPP on day 1 after plantar incision surgery (a 1-cm longitudinal incision was made through the skin of the left hindpaw and the plantaris muscle was elevated and incised longitudinally. The cut skin was stitched with two 5-0 nylon sutures and the wound site treated with neomycin.). C) Sumatriptan (0.6 mg/kg, s.c.) administered 2.5h prior to popliteal fossa lidocaine did not prevent PNB-induced CPP.