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TRPV1 and MOR working in tandem: implications for pain and opioids use

Nasser Abdullah[1] and Christophe Altier[1]

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Opioids are widely used medications for the relief of moderate to severe pain. While they remain one of the strongest analgesics for pain associated with cancer, trauma, or surgery, prolonged treatment often comes with undesirable side effects, including analgesic tolerance that causes dose escalation and addiction.

Three opioid receptors: mu-, delta-, and kappa-opioid receptors (MOR, DOR, and KOR, respectively) are found in the afferent pain pathway and participate in opioid-induced analgesia [1]. These receptors respond to exogenous (i.e morphine) and endogenous opioids (β-endorphin, enkephalins, and the dynorphins) that exert efficient inhibitory control of pain at sites of inflammation and in the central nervous system. The endogenous opioid system represents an evolutionarily important pain-coping strategy during tissue healing and several studies have shown that opioid receptors on afferent nociceptors respond to peripherally acting endogenous opioids released by immune cells, including $CD4^{+}$T cells that are recruited in the later phase of inflammation [2]. Overall, pain sensitization and opioid signaling appear intertwined in the establishment of chronic inflammatory pain. Activation of the mu-opioid receptor (MOR) by opioids results in the binding of β-arrestin2 to the receptor. This interaction prevents receptor signaling, and elicits desensitization, which in turn reduces the pain-relieving effect and requires increased opioid administration, enhancing the unwanted side effects of MOR activation [3]. Previous work reported an improvement of the opioid therapeutic window in acute inflammation, suggesting a mechanism by which inflammation renders opioid receptors to be more responsive [4]. We recently identified the transient receptor potential vanilloid type 1 (TRPV1), a main target of inflammatory mediators, as a central hub protein that primes pain-relieving effects of opioids. MOR is predominantly expressed in $TRPV1^{+}$ nociceptors and chemical stimulation of the TRPV1 channel was found to prevent G protein-coupled receptor kinase 5-dependent phosphorylation of agonist-bound MOR [5]. We found that activation of TRPV1 diverts the MOR effector β-arrestin2 to the nucleus, and this process coincides with enhanced mitogen-activated protein kinases (MAPK) signaling. With β-arrestin2 removed from the membrane-anchored MOR, the receptor is free of β-arrestin2 and hence unable to desensitize and internalize. We next used the complete Freund's adjuvant (CFA) model of chronic inflammatory pain to show that TRPV1 knockout mice do not exhibit endogenous opioid analgesia during resolution of inflammation. Finally, using morphine-treated animals, we found that absence of TRPV1 expression promotes peripheral opioid receptor desensitization. Altogether, our findings suggest that agonists of TRPV1 prevent β arrestin2-biased signaling of MOR, which enhances analgesia by maintaining peripheral opioid receptor function (Fig. 1) [6]. As chronic inflammatory conditions like arthritis or inflammatory bowel diseases are often associated with persistent pain, further studies will reveal whether the dysregulated interplay between TRPV1 and β-arrestin2 contributes to the transition from acute to chronic pain.

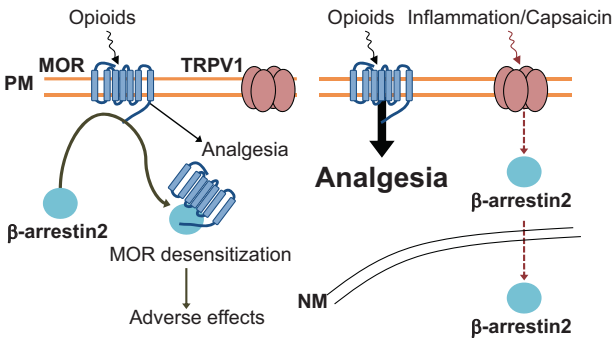

Fig. 1 Illustration of TRPV1–MOR interplay with (right) and without (left) inflammation. MOR desensitization, mediated by β-arrestin2 recruitment to the receptor, promotes analgesic tolerance. Activation of TRPV1 with capsaicin, or during inflammation, prevents β arrestin2-biased signaling of MOR, and thus enhances analgesia

With current research efforts focused on optimizing new types of opioids that circumvent the adverse side effects, these findings could lead to new combination therapies using TRPV1 agonists like vanilloids and cannabinoids as effective analgesics that may also be useful to prevent opioid tolerance.

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[1]Department of Physiology and Pharmacology, Inflammation Research Network, Snyder Institute for Chronic Diseases and Alberta Children's Hospital Research Institute (ACHRI), University of Calgary, Calgary, AB T2N 4N1, Canada
Correspondence: Christophe Altier (altier@ucalgary.ca)

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ADDITIONAL INFORMATION

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Towards objective definition of psychopathology in post-traumatic stress disorder

Amit Etkin [1,2,3]

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Owing to their reliance on imprecise clinical phenotypic definitions, current psychiatric diagnoses capture a broad range of neurobiological alterations across patients. The difficulties that arise from these definitions are particularly striking for post-traumatic stress disorder (PTSD). For example, the revision of its diagnostic criteria from DSM-IV to DSM5 resulted in only a ~ 50% overlap in case definition [1]. One way to overcome challenges inherent to these clinical definitions is to anchor patient definitions in objectively quantifiable measures [2].

To identify biologically and clinically meaningful PTSD subtypes, we began with the perspective that cognitive task behavior may be a particularly useful way to anchor patient phenotypes so that they are both objective and face-valid [3]. Within cognition, verbal memory is the domain most impaired in PTSD patients on average [4]. We therefore treated verbal memory in a normative perspective, dividing patients based on whether they performed within or outside the healthy norm, and examined resting-state functional magnetic resonance imaging (fMRI) network connectivity to understand mechanisms involved with differences in memory [3]. This is akin to a typical medical test, which are often framed within a normative perspective. We found, and then replicated (total $N = 357$), that after correction for multiple comparisons, connectivity in one brain system (the ventral attention network; VAN) was reduced only in PTSD patients with impaired verbal memory, relative to either controls or patients with intact memory.

Critically, moreover, memory and VAN connectivity predicted treatment outcome, thus demonstrating clinical relevance, despite the discovery of the memory–VAN connection coming out of a mechanistic characterization rather than one primarily targeting treatment prediction [3]. Patients in one of the samples went on to receive either prolonged exposure psychotherapy, a gold-standard treatment for PTSD, or a wait list intervention control. Those patients with impaired memory and VAN connectivity failed to respond to prolonged exposure (and did not differ in the wait list arm), whereas those without both abnormalities responded well. Finally, to understand how these insights may be useful in driving new therapeutics, we used simultaneous non-invasive transcranial magnetic stimulation and electroencephalography (TMS/EEG) to map the brain's response to single TMS pulses at various locations and implicated a region in the right prefrontal cortex [3].

These results suggest that by anchoring on an objective measure (i.e., verbal memory), clinically and mechanistically meaningful biological differences can be observed and replicated. The TMS findings further suggest an avenue for developing novel interventions for memory–VAN impaired patients, by targeting the right prefrontal cortex.

More broadly, these findings open up a path for transcending traditional clinical phenomenology and grounding clinically meaningful case definition in observable biomarkers. To ultimately impact clinical care, we anticipate that tools such as EEG (a cheaper and more clinic-ready tool than fMRI) and machine learning (to make relevant brain signatures more robust) will be required. Nonetheless, our results suggest that it is more a question of how, rather than whether, these types of biomarkers could transform diagnosis and treatment in psychiatry.

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[1]Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA, USA; [2]Wu Tsai Neurosciences Institute, Stanford University, Stanford, CA, USA and [3]Veterans Affairs Palo Alto Healthcare System, Sierra Pacific Mental Illness, Research, Educatioand Clinical Center (MIRECC), Palo Alto, CA, USA
Correspondence: Amit Etkin (amitetkin@stanford.edu)

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