Do endogenous opioids mediate or fine-tune human pain relief?

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This is a commentary on *Endogenous opioids contribute to the feeling of pain relief in humans* by Sirucek et al, In Press, Pain. We discuss how effects of different magnitudes from human opioid antagonist studies can be interpreted and how the results inform us on the role of the endogenous mu-opioid system for pain relief and other affective processes in humans.

Opioid analgesics bind to the brain's mu-opioid receptors. Endogenous activation of these receptors is also thought to relieve pain. For instance, Zubieta and colleagues [26] found that the higher the endogenous mu-opioid response to prolonged experimental pain in pain-sensitive regions such as the thalamus and insula, the lower the pain was reported by the participants. Painful events are thought to trigger release of endogenous opioids as a regulatory, opponent mechanism [15,22]. When endogenous mu-opioid activity is pharmacologically blocked by an antagonist, this regulatory mechanism is inhibited. At first consideration, it may therefore seem surprising that opioid blockade was not found to increase pain by Sirucek et al. in this issue [21].

Automatic and universal opioid pain regulation in humans?

However, using hidden as well as open infusion of the non-specific opioid antagonist naloxone in dental surgery patients, Levine and Gordon concluded as early as 1984 that increased pain after open naloxone administration was “due to naloxone antagonism of placebo-induced analgesia and [] not an effect of naloxone on the natural history of post-operative pain” (p755, [16]). More recent antagonist studies have produced mixed results, with some studies reporting higher pain after opioid antagonism [1] and others finding no reliable change compared to an inactive drug [2,3]. Considered together, the available data does not support the existence of a universal and automatically triggered opioid-mediated pain regulatory mechanism in the human brain [25].

Could it be that only severe, prolonged or clinically relevant pain triggers such opioid-mediated regulation? For instance, the molecular imaging studies that have linked endogenous mu-opioid activity with downregulation of pain have typically induced sustained facial pain of 20 minutes or more [e.g. 26]. However, studies of post-surgical [16] and chronic low-back pain [3] have reported comparable pain levels after opioid antagonism relative to placebo, suggesting that prolonged clinical pain does not necessarily trigger opioid pain regulation. More well-controlled research is needed to determine the conditions under which endogenous opioids relieve pain in the human brain.

Does opioid antagonism decrease the experience of relief?

The term pain relief refers to two separable experiences: reduced pain, and the experience of relief itself. Changing the speed of pain reduction illustrates the difference: a quick decrease achieves homeostasis faster and is typically experienced as more marked and rewarding than an equally large, but slower decrease of pain [15]. Relief can also be induced by the removal of *threat* of pain, i.e. without any relief from physical pain. To measure the relief experience, studies often ask participants to rate its intensity or pleasantness on a 0-100 visual analogue scale (VAS). Participants in Sirucek et al's study rated pain in some trials; in others they were asked to report on their experience of relief [21]. A cooling stimulus (25 °C) was applied to the capsaicin-treated skin after 30 or 60 seconds of heat calibrated to induce high pain. This approach speeds up the pain reduction and intensifies the

relief [5], akin to the pleasant cooling effect of a cold shower on a sunburned back. In line with the authors' hypothesis, naltrexone significantly reduced both the intensity and pleasantness of cooling-induced relief. The size of the reduction was modest, 5-10 points on a 0-100 VAS (see also Figure 1). What does this unstandardized effect size tell us about the role of endogenous opioids for pain relief?

Opioid fine-tuning of relief pleasantness

First, Sirucek et al convincingly demonstrate that the experience of relief after pain offset partly depends on endogenous opioid signalling. Second, they show that much of the participants' experience of relief is opioid-independent. In line with our lab's [7,8] and other opioid drug studies investigating reward responses [4], full mu-opioid blockade reduced the pleasant experience but did not *eliminate* it. Together, these results point to a

role of endogenous mu-opioids in fine-tuning pleasant experiences from both negative and positive reinforcers. That is, blockade of 90% or more of mu-opioid receptors by naloxone [17] or naltrexone [13] may remove some enjoyment or hedonic gloss [10], without eliminating participants' ability to judge the overall reward value of a stimulus.

Fine-tuning or full opioid-dependence?

In contrast to the modest reductions reported for the experience of relief and reward in humans, naloxone was found to completely block relief-related hypoalgesia [2], although post-task subjective ratings of relief were unaffected. Complete elimination of behaviours after opioid blockade is also reported in many rodent studies. Intra-ACC blockade with naloxone fully eliminated relief-induced conditioned place preference and dopamine release [18]. Similarly,

How to interpret results from an antagonist study

- Assuming appropriate study design (blinding, placebo control, sufficient power etc.)

Figure 1. How different type of opioid-antagonist effects can be interpreted depends on the degree of mu-opioid receptor blockade. The interpretations depicted assume adequate study design, including double-blind, randomized, counterbalanced testing, valid measurements, and appropriate statistical power. The findings from Sirucek et al in this issue included a null effect for full blockade of mu-opioid receptors on pain ratings (indicating opioid-independent pain processing) and a modest effect of opioid antagonism on ratings of relief from cooling skin after pain (consistent with opioid fine-tuning of relief).

preventing mu-opioid signalling eliminated the effects of food deprivation on measures of food palatability [24] and consumption [6]. Such examples of full opioid-dependence may point to a fundamentally different role of endogenous opioid signalling in rodents versus humans. It is also possible that in humans, mu-opioids only fine-tune valuation of rewards, yet are *necessary* for certain types of hypoalgesia [2,25]. In general however, current evidence favours a role of human endogenous opioids in fine-tuning responses to both rewards and pains. With some exceptions, hypoalgesia induced by placebo treatment, stress, or rTMS is typically reduced but not eliminated by opioid antagonism [9,19,23].

Interpreting results from opioid antagonist studies

Two considerations are key for interpretation of modest or null effects in antagonist studies assessing endogenous opioid function (Figure 1; see also [14] for a checklist of study design requirements): 1) Did the study employ full mu-opioid receptor blockade (90-100% binding)? With partial blockade, a weak/null effect might simply reflect that the behaviour relies on a subset of mu-opioid receptors unbound by the antagonist. Hence, only full blockade studies can reliably determine opioid-independence or opioid fine-tuning of an effect. 2) Standard frequentist statistical tests do not permit rejection of the hypothesis (or acceptance of the null hypothesis). In other words, a weak/null effect could result either from a true weak/null effect, or due to insufficient statistical power. Sirucek et al. commendably employed Bayesian statistics to probe the generalisability of their null effect of antagonism on pain¹. Across pain measures, the tests provided anecdotal or moderate support for the “true” absence of a drug effect. Displaying all data points and otherwise increasing transparency, as did Sirucek et al, also aids readers in making their own judgment about the data and results. In sum, this full opioid blockade

data supports the interpretation that endogenous mu-opioids did not modulate pain ratings. Another recent study illustrates the challenges of interpreting null findings when statistical power is limited. In a commendable translation of rodent research to humans, Fuss and colleagues used naltrexone to test the opioid-dependence of runner’s high euphoria [20]. Placebo-treated participants reported a running-induced increase in euphoria of ~24 points (0-100 VAS). The comparable mood boost in the naltrexone group was of ~18 points [20]. Hence, runner’s high was not eliminated by full mu-opioid blockade, and the group difference was not statistically significant. The authors conclude that runner’s high is opioid-independent. Is this interpretation supported by the data?

It is clear that substantial runner’s high can be observed after full opioid blockade. Yet, the unstandardized effect size (~6-point reduction in euphoria) matches the modest size of fine-tuning effects reported in the studies reviewed above [2,4,7–9,21]. The study only had statistical power to reliably detect larger effects, and did not report equivalence tests. Hence, it seems likely that a larger study might find support for endogenous mu-opioid fine-tuning of runner’s high similar to opioid effects on relief after pain.

Reframing endogenous opioids as a system for fine-tuning human affect

The evidence from human studies using opioid antagonism indicate a role for endogenous mu-opioids in fine-tuning rather than fully mediating responses to pain and reward. These relatively modest effects, where e.g. pain relief is modulated but not eliminated by full opioid blockade, are somewhat surprising in light of popular conceptualisations of endogenous opioids as the brain’s own pain relief and/or feel-good system. They also contrast with the complete elimination of effects observed in some rodent studies, e.g. relief-related dopamine release [18]. Nevertheless, such opioid-mediated fine-tuning

¹ For those more comfortable with frequentist statistics, equivalence testing is a good alternative to Bayesian analysis of null results [12].

effects may significantly affect human experience and behavior. Dysregulation of such fine-tuning over time may substantially affect wellbeing [11]. In sum, it is likely that the mu-opioid receptor system works in concert with other neuromodulatory hormones and transmitters to produce and fine-tune hedonic experience of both pains and pleasures.

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