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Opioidergic Tone and Pain Susceptibility: Interactions between Reward Systems and Opioid Receptors

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Defining an easily measurable sensitive phenotype for pain susceptibility is clearly one of the great steps forward in the pain field. The paper by Nees and colleagues¹⁸: “*Brain substrates of reward processing and the μ -opioid receptor: a pathway into pain?*” is a novel and important contribution to the field in this regard, combining functional imaging and genetic data in over 600 healthy subjects to evaluate the development of pain in previously pain free individuals. The paper poses interesting questions about the predilection of pain which has been a topic of interest for a number of years related to bio-psycho-social issues including psychological (fear of pain²⁴, catastrophizing¹⁹), functional imaging (specific reward networks⁵), or genetic markers^{10, 23} in the evolution of pain or possibly pain chronification. The paper addresses the interactions of two main processes: (1) the contributions of single nucleotide polymorphisms (genetic) of the μ receptors on pain and (2) the ‘biomic’ status (state dependent¹²) of brain reward systems and their interactions with SNP status of individuals that may contribute to predicting later onset of pain (i.e., resilience).

Opioid Receptor SNPs and Pain

Opioids are ubiquitous and found throughout the brain, including regions involved with nociception/pain transmission¹², placebo and reward and aversion processes⁷. The individual's susceptibility to pain and pain chronification is dependent on genetic and other factors that may be lumped into the notion of ‘resilience’ to the evolution or chronification of pain. Alterations in opioid receptor interactions with endogenous or exogenous opioids contribute to an overall ‘opioid tone’ that depends on receptor subtype and receptor density. The latter may contribute to analgesic (e.g., endogenous analgesia¹⁷), placebo²⁷ or hyperalgesic/pain (e.g., withdrawal¹, chronic opioid administration⁴, sex differences¹⁴, nocebo²²). Thus the level and type of opioid present may contribute to a basal state or ecosystem that can be tipped in susceptible individuals. The recent imaging work has shown significant alterations of brain structure and function in individuals taking opioids^{25, 28} suggesting, perhaps, that opioidergic drive can contribute to significant differences in phenotype, including the response to pain.

Single nucleotide polymorphisms (SNPs) are associated with differences in pain perception^{13, 20} including rs6746030 (SNP in sodium channel Nav1.7 SCN9A gene²⁰). Here two other SNPs are evaluated in the context of pain onset over time: (1) rs179971 which linked to the mu opioid receptor gene OPRM1, and is associated with alcohol craving²⁶, and response to mu opioids, including the increased use of opioids²¹; and (2) rs563649, also

associated with OPRM1 and may be a predictor of persistent pain¹⁵. The authors report correlations of OPRM1 allele carriers indicating that rs179991 is not related to pain complaints, while rs563649 was related to later pain complaints. T allele carriers having more pain than C-allele carriers, and brain responses (see below) during reward were also related to the rs563649 SNP in T allele carriers. Thus, rs563649 SNP analysis may serve as a marker for the evolution of pain with time.

The “Biomic” status of the Brain: Reward Systems Tone

The nature of the brain’s state and its response to the response and development of pain depends on chemistry, functional and structural connectivity – predetermined by genetic, social and other biological processes. In the paper published in this volume, the authors evaluate reward circuitry in a pediatric population at two time points. While a number of interactions between the SNPs and brain functions are discussed, the main findings are summarized here.

The authors report that the BOLD signal in the dorsal striatum in response to reward feedback predicted magnitude of pain level 2 years later, independent of the genetic SNPs (rs1799971 and rs563649). However, later pain was predicted by the BOLD response in the periaqueductal gray (PAG) and ventral striatum in response to reward feedback in TC/TT carriers of rs563649¹⁸. The differences in brain responses are intriguing: The dorsal striatum (caudate nucleus and the putamen) is involved in decision making “*through the integration of sensorimotor, cognitive, and motivational/emotional information*”³. The ventral striatum (nucleus accumbens) has been implicated in reward and aversion⁵ and its level of functional connectivity with dorsolateral prefrontal cortex, implicated in predicting pain chronification² and in differences in pain intensity¹⁶. Thus, both these regions are involved in pain and analgesia processing as assessed⁹. Thus the author’s findings are consistent with our current understanding of striatal involvement in pain. The PAG is involved in a number of integrated functions⁶. The role of the PAG in predicting pain response is perhaps best understood in the context of activation in modulating the pain processing with the increased pain observed in the older group; and here further supported by the association of a decreased opioid concentrations in T-allele carriers of rs563649.

Going Forward

The report provides some intriguing questions that include, but are not limited to: (1) Is Opioidergic Tone a real indicator of pain susceptibility? (2) Can this phenotype be used to evaluate and understand responders from non-responders? (3) Can the phenotype be used to evaluate those at risk for chronification (resistance)? (4) Can the phenotype predict whether or not opioid non-responders or patients receiving opioids will experience worsened pain? (5) Does the presence of the rs563649 allele groups contribute to more rapid or persistence of pain chronification? (6) What happens to these patients over time? (7) How do these reward systems interact with anti-reward systems^{8, 11}? There are some caveats to the study, including evaluating differences over longer periods of time, and underlying mechanistic process. It would seem that this study has the potential of unleashing truly useful tools in the clinic. This will obviously depend on more studies, but the door has been opened for an

intriguing process that may have a significant influence on improving our approach to evaluating and treating patients with pain.

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