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A life switch in pain

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Perhaps for the purpose of increased self-protection and survival from potentially noxious conditions, newborns and young children, whose ability to predict and avoid such harmful conditions is still developing, have significantly lower pain threshold and exaggerated pain responses compared to adults. This developmental difference in pain sensitivity, which has been documented in both humans and animals, has significant clinical relevance. The development of pharmacologically targeted pain management strategies for infants and children must take these differences into account. It is thus particularly important to have a comprehensive understanding of the developmental changes in receptor pharmacology and synaptic connections of the central pain-modulating circuits during the postnatal period. Unfortunately, research in this area is quite limited.

Neurons in the rostroventral medulla (RVM), the axons of which project to the spinal cord dorsal horn, are a major source of controls for the transmission of pain messages to higher brain centers [2]. Importantly, this RVM-mediated descending pain control network is bidirectional, having both pain-inhibiting and pain-facilitating actions on spinal pain transmission [5]. Whether the predominant influence of this descending pain control system is inhibitory or facilitatory is dependent on behavioral state [4,7]. For example, during chronic pain conditions, the RVM pain-facilitating pathways are abnormally hyperactive, and contribute to sensitized pain behaviors, such as hyperalgesia [9]. In this issue of *Pain*, Hathway and colleagues turned their attention to the differential controls exerted from the RVM in preadolescent and adult rats. They present interesting results that reveal a novel contribution of the RVM pain control system in regulating pain sensitivities and responses to opioids at different development stages [6]. The authors report that in preadolescent rats (postnatal day 21), the descending RVM influence on pain is predominantly facilitatory. This unidirectional action contrasts significantly with the coexistence of facilitatory and inhibitory effects in adults (postnatal day 40). Most surprisingly, the authors found that microinjection of a highly selective mu-opioid receptor (MOR) agonist (DAMGO) into the RVM, which is powerfully analgesic in adult animals, has an opposite, facilitatory effect on pain responsiveness in adolescent rats. Furthermore, the age-dependent emergence of descending inhibitory controls from the RVM appears to be dependent on normal CNS opioid activity. Thus, blockade of endogenous opioid circuits with an opioid antagonist prevented maturation of the descending inhibitory system. By contrast, administration of an exogenous opioid accelerated the appearance of inhibitory controls. These findings indicate an intriguing developmental change in RVM control of spinal pain transmission. In other words, there appears to be an opioid receptor-dependent functional switch in RVM control of pain responses during development, from predominant facilitation to balanced inhibition and facilitation. The authors hypothesize that the predominantly facilitatory RVM influence

in young animals underlies the higher pain sensitivity and exaggerated pain responses observed in infants and young children.

While the mechanisms underlying the switch from facilitation during development are not known, the fact that the switch is influenced by endogenous and exogenous opioids suggests that the shift in the direction of the RVM pain controls is activity-related. Based on current literature, the changes responsible for the shift are likely multifaceted, involving developmental alterations at the levels of receptor and channel pharmacology, synaptic connections among functionally distinct neuronal classes within the RVM circuit, cellular expression and distribution of opioid receptors in the neuronal network, and activity-dependent alterations in epigenetic control of genes that code for responsible signaling proteins. First, at the receptor and channel level, the major effect of mu opioid receptor agonists in the adult RVM is presynaptic inhibition of inhibitory GABA inputs onto presumably pain-inhibiting neurons, causing disinhibition, or activation, of these neurons and descending pain inhibition [8]. Current evidence does not support a direct excitatory effect of MOR agonists in preadolescent animals. Therefore, the DAMGO-induced pain-facilitating effect observed in the Hathway study in preadolescent rats could be mediated by mechanisms downstream from MOR, at MOR-coupled signaling pathways and ion channels. In this regard, it is significant that GABAergic synaptic transmission, which is inhibitory in the adult, is excitatory in immature neurons of the developing brain [1,3]. If this excitatory effect during development is also true for RVM GABA circuitry, then the presence of some excitatory GABAergic synapses could increase the excitability of the pain-inhibiting neurons, which would counteract the altered matured descending pain-facilitating system that appears to predominate in the developing RVM. Thus, DAMGO inhibition of the excitatory GABA synaptic activity would inhibit, rather than disinhibit (i.e. activate, as occurs in the adult), neurons of the descending inhibitory system. In other words, DAMGO inhibition in the developing animal would indeed shift the balance towards descending pain facilitation. Although the similar inhibitory effects of the GABA_A receptor antagonist gabazine in preadolescent and adult rats, described in the Hathway paper, argue against this hypothesis, more detailed electrophysiological studies on GABA synaptic transmission in the developing RVM are warranted. It will also be of interest to examine the effects of GABA_A receptor antagonists in awake, freely moving animals, to exclude the influence of anesthesia on GABAergic transmission. Second, at the synaptic and neuronal network level, both functional GABA_A receptors and the MOR may undergo dynamic changes with age, through mechanisms of membrane trafficking (with or without changes in total protein) and transcriptional control of gene expression. Depending on the subtype/class of RVM neurons in which such dynamic changes occur, there could be significant alteration of the overall dominant effects of GABA transmission and MOR agonists on pain behaviors.

Unquestionably, the authors' most intriguing finding is that the maturation of descending inhibition depends on opioid activity. While endogenous opioid-induced trophic effects on synaptogenesis are certainly possible, other scenarios can be envisioned. For example, the developmental changes could be mediated by activity-dependent epigenetic mechanisms that control transcriptional activity of the genes that encode proteins required for the maturation of RVM descending inhibition. In this respect, it can be speculated that the greater pain sensitivity in the neonate and in very young animals shares some common mechanisms with those that underlie the development of chronic pain after injury. For example, persistent pain is associated with a shift of RVM pain controls to a facilitatory mode [9] and as we recently reported, this is likely through epigenetic regulation of RVM GABAergic neurotransmission [10]. As there are pharmacological tools that can influence epigenetic regulatory mechanisms, it will be of great interest to address their contribution to the development switch that Hathway and colleagues describe. Success in that endeavor could contribute significantly to the improvement of pain management for pediatric patients.

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