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Current Opinion in Physiology

The changing role of descending control of spinal nociception over postnatal development

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Pain is a powerful survival signal, alerting the individual to damaging environmental stimuli. Neonatal and juvenile animals have significantly lower thresholds for detecting these noxious stimuli and respond in an exaggerated manner compared to adults. This review highlights advances in our understanding of how supraspinal centres control the excitability of the spinal dorsal horn (DH). These descending control systems, in adults, can facilitate or inhibit nociception, thereby increasing or decreasing the pain an individual feels. Until recently the contribution of these systems to pain in early life was overlooked and it is only in the last 10 years that significant work has been undertaken. We briefly summarise recent advances in our understanding of the physiological properties of the rostroventral medulla (RVM), the roles of the endogenous opioid and endocannabinoid systems, the impact of pain on the maturation of these systems and the importance of these systems in humans.

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Current Opinion in Physiology 2019, **11**:93–96

This review comes from a themed issue on **Physiology of pain**

Edited by **Lucy F Donaldson** and **Cheryl L Stucky**

For a complete overview see the Issue and the Editorial

Available online 27th August 2019

https://doi.org/10.1016/j.cophys.2019.08.003

Introduction

The dorsal horn (DH) of the spinal cord is the primary site for integration of somatosensory information in the central nervous system (CNS). Its principle roles are to elicit nocifensive reflex behaviours to protect the organism from external environmental threats and to relay information to the brain. The processing of noxious information in the DH is significantly different in early life to that in adulthood [1] with neonates and young animals being hyperexcitable, having lower sensory thresholds to evoke exaggerated and uncoordinated reflex behaviours [1]. The characteristics of these behaviours reflect not just the magnitude and quality of incoming somatosensory information but also the excitability of the DH itself. Increased DH excitability not only leads to lowered thresholds and larger and longer reflex behaviours, but it also leads to increased perception of pain supraspinally [2]. In adults DH excitability is modulated via descending projections from the brainstem, most notably the rostroventral medial medulla (RVM) but also including the hypothalamus and locus coeruleus. These pathways form the basis for endogenous pain control systems that utilise endogenous opioid peptides, endocannabinoids and monoaminergic neurotransmitters. A role for descending control of DH excitability from the RVM in neonatal and juvenile animals was first demonstrated in 2009 [3]. Unlike in the adult, stimulation (electrical or pharmacological) of the RVM is only able to facilitate DH excitability, descending inhibition does not emerge until the 5th–6th postnatal week in rats. Since then significant progress has been made in understanding how these systems change over early life. In this short review we summarise work from 2009 to present. We have undertaken a semi-systematic approach to identify papers for inclusion. Using PubMed and Web of Science we identified common papers using the search terms 'Pain' and 'Neonate or development or postnatal' with subsearches for 'opioids', 'cannabinoids', 'RVM' or 'PAG'.

The spinal dorsal horn

The DH of the spinal cord, is a main site of action in the top–down endogenous pain control system, as the anatomical site with the first synapse between peripheral and central nervous systems. It is widely accepted that the DH continues to develop and mature during early life and that interruption to this, for example, through early life pain, can have long lasting effects into adulthood [2]. Whilst specific changes in the DH that occur over postnatal development will be discussed elsewhere in this issue it is important to remember that changes in the physiology of the DH will occur concurrently with changes in descending pain control. Perturbation of DH maturation can significantly alter the maturation of descending control systems.

Supraspinal structures

Ascending and descending projections link the spinal cord with supraspinal sites including regions well known to be associated with pain processing such as the RVM and periaqueductal grey (PAG). These supraspinal sites undergo significant maturation during postnatal development with the majority of recent work focusing on the RVM-spinal part of this system. At postnatal day (P) 8-P10

the RVM-spinal system is still immature; the RVM and PAG do not respond to nociceptive input, there is tonic descending spinal facilitation from the RVM, and a lack of glutamatergic drive. However, by P12 the RVM and PAG do respond to nociceptive input and glutamatergic drive in the RVM-spinal system is detected by P21 [4]. This is a similar age to when the proportion of descending serotonergic neurons from the RVM increase (P10–16) which precedes a switch from descending serotonergic facilitation to both tactile and noxious activity via 5-HT3R to a differential descending serotonergic control, in which tactile stimulation is linked to facilitatory processing and pain is linked to inhibitory processing [5•].

Devonshire *et al*., propose that a change in the integration of RVM-spinal projections occurs during postnatal maturation of descending control rather than the properties or proportions of the ON and OFF cells found within the RVM [6]. In line with this, the resting membrane potentials of RVM ON and OFF neurons do not change between immature (P10–21) and mature (P30–90) rats, however, higher levels of spontaneous firing and higher levels of spontaneous GABA release were found in immature compared to mature RVM neurons [7]. This is accompanied by an age-dependent difference in opioid mediated inhibition of GABAergic mIPSCs suggesting that opioid receptors are better able to inhibit GABA neurotransmission with increased age [7].

Postnatal maturation occurs in other supraspinal regions involved in pain processing such as the primary somatosensory cortex (S1). Here it has been demonstrated that despite the overall power of electroencephalogram (EEG) responses to noxious thermal stimulation of the hind paw being the same in P21 and P40 rats the distribution is refined with age; transitioning from a generalised response across the whole frequency spectrum in juveniles to a specific increased in the theta band (4–8 Hz) in adults [8]. Further studies in freely behaving rats shows that early life incisional injury which decreases hindpaw pain thresholds at all ages alters gamma band (20–50 Hz) energy only from three-weeks of age and not in younger pups [9].

Endogenous opioid and endocannabinoid neuromodulatory systems in descending control

Opioids and cannabinoids have been widely associated with analgesia for centuries. These drugs rely on endogenous pain control systems which utilise opioid peptides and endocannabinoids respectively, to provide pain relief, as well as other having other psychoactive properties [10]. Previously we have shown that endogenous opioid peptides are necessary for the maturation of RVM mediated control of DH excitability [11]. Within the mid-brain PAG and the RVM administration of mu-opioid receptor agonists provokes increases in DH excitability in contrast to decreases seen in adults [12,11] within both of these structures an opioidergic tone exists which when removed lowered mechanical pain thresholds in juvenile rats [12]. These changes are associated with alterations in the expression of opioid receptors and opioid peptides in PAG and DH [12,13]. The mechanisms by which opioids mediate these opposing actions at different life stages are still unknown but may reflect alterations in the intracellular signalling systems engaged by the receptors which promote cellular excitability.

Endocannabinoidergic systems are also fundamentally altered early in life compared to adults [14,15]. Kwok *et al*. have shown that substantial functional changes exist in the PAG and RVM when cannabinoid receptor agonists or antagonists are microinjected into these structures at different postnatal ages [15], again these are associated with changes in endocannabinoid receptors and synthetic and degradative enzymes as well as tissue levels of endocannabinoid lipid-derived neurotransmitters. These rodent data were corroborated with studies in post-mortem human brainstem tissue, in which age-related alterations in transcript levels of endocannabinoid receptors were demonstrated [15]. Recent data were from a clinical case involving an adult female with congenital insensitivity to pain due to microdeletions in a gene FAAH-OUT [16••]. This mutation significantly elevated circulating (and presumably central) concentrations of fatty-acid amide endocannabinoid compounds (such as anandamide and palmitoylethanolamide) which significantly increased sensory thresholds in this person. This finding demonstrates the power of endocannabinoid neurotransmission in regulating pain processing. Together with animal data this human study indicates that further developments within our understanding of endocannabinoid signalling may lead to new age-appropriate analgesic approaches.

The impact of stress in early life on later life pain processing

Immature animals are capable of experiencing significant stress associated with parental (usually maternal) separation, pain and environmental factors. Within the pain literature over the last five years the main sources of stress which have been investigated which impact on pain sensitivity in later life have focussed on maternal separation in early life [17], surgical skin wounding [18,19], needle pricking [13,20,21] or experimental inflammation [22]. Maternal separation is known to lead to significant disruptions to adult neurological processing [23]. Further, exposure to early life stress is a risk factor for developing disorders of the hypothalamic–pituitary–adrenal (HPA) axis [24] (for review see Ref. [25]). Maternal separation leads to altered sensory thresholds and pain sensitivity and these changes have recently been associated with changes in oxytocinergic systems [17]. Mice separated from their mother had decreased thresholds in adulthood which was reversed by intracerebroventricular (i.c.v.) administration of oxytocin, an effect which was also efficacious in reversing

acute stress related changes in pain sensitivity when mice were restrained. Stress though can occur following physically damaging events such as through surgery or through medical procedures such as repeated hypodermic needle insertions. Davis *et al.* [20] have shown that repeated needle pricks caused significant changes in somatosensory and affective behaviours in rats later in life. Similarly de Carmo *et al.* [21] have shown similar changes in sensory processing accompanied by alterations in motor function as indexed by grip strength. These changes have been associated with altered responses to further re-injury in adulthood [13,26] and that this is the result of altered mu-opioid receptor expression in the DH. Endogenous opioids have previously been shown to be essential for the maturation of descending control emanating from the RVM [3,11] and that a critical period in the fourth postnatal week exists for normal adult, bi-phasic control of DH excitability to mature [11]. Early life surgical injury has been shown to cause a significant reduction in sensory thresholds in adulthood in humans [27,28••,29•]. Using surgical skin wounding in rats as a model of human clinical experience it has been shown that this results in long-term body wide hypoalgesia in rats which is directly related to the maturation of the RVM [18] and enhanced hyperalgesia following re-injury [30]. However, another study showed that a similar experimental injury caused basal hypersensitivity later in life [19] and that there were sex-dependent elements to this with males being more susceptible. Whilst the differences in outcomes is difficult to explain and beyond the scope of this review these data point to changes in supraspinal centres that directly or indirectly influence nociception via spinally projecting pathways. Importantly these early life events can alter adult pain experience in both the sensory and affective neurological domains.

Human neonates and descending control

The majority of studies discussed so far have been in laboratory rodents but evidence for similar changes in endogenous, descending pain control systems in humans also exists. In comparison to adults, infants display a number of differences to adults in cortical and spinal activity with early life exposure to injury resulting in a number of adverse outcomes in later life [28••].

Since 2014 a number of advances have been made in our understanding of these differences. Goksan *et al.* demonstrated that the strength of functional connectivity within descending pain modulatory system (including the PAG and the medulla) influences noxious-evoked brain activity in new-born infants, suggesting that this system may regulate the magnitude of noxious-evoked brain activity [31•]. Recent studies have additionally supported that nociceptive brain activity in infants is not stable throughout infanthood, with a separation between the increase in magnitude of nociceptive brain activity with gestational age, and spinally mediated withdrawal reflexes which decrease in magnitude and are refined over this period [32•]. Fabrizi *et al.* have shown that infants and adults share many aspects of nociceptive responses in the brain but that there are significant differences in specific aspects of EEG responses (a long-latency fast delta band response present in infants that is absent in adults) which has an extensive topographic representation across the brain [33••]. This widespread activity is more likely to occur in female infants, regardless of age at which they were born [34]. These early sex differences are particularly relevant given the lack of sex differentiation in the majority of neonatal rodent studies. Further studies have shown that whilst cortical activity and an individual's behaviour usually correlate this is not the case when stress levels in an infant are raised [35]. This significant effect of stress indicates an important contribution of the HPA axis in pain responses in infants presumably mediated via descending control of DH activity. Although touch-based techniques (e.g. kangaroo care) have been demonstrated to exert positive effects on pain-related behaviour in humans, it was unclear whether these effects could also mediate changes in nociceptive brain activity [36]. Gursal *et al.* demonstrated that stroking at 3 cm/s affects noxious-evoked brain activity in infants during a painful clinical procedures, providing neurobiological evidence for the efficacy of non-pharmacological interventions for clinical procedures [37•]. Whilst the majority of these studies have not directly addressed changes in descending control (with the notable exception of Ref. [31•]) evidence for widespread changes in brain activity related to painful stimuli will impact upon endogenous pain control systems.

Conclusions

Work since 2009 has determined that the brain is able to powerfully modulate pain responses in early life in both humans and laboratory animals. The importance of the maturation of these systems in not just modulating acute pain responses but also in the long-term health and well-being of individuals is being revealed. As we increasingly recognise pain in early life as being substantially different to that in adults and therefore requiring tailored approach to its management, future research in this area must seek to understand how descending control systems can be manipulated and exploited to provide age-appropriate analgesia.

Conflict of interest statement

Nothing declared.

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- • of special interest
- •• of outstanding interest

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