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AN UPDATE ON PAIN PHYSIOLOGY: THE RELEVANCE OF CRAIG'S AND JÄNIG'S HYPOTHESES FOR HYPNOTIC ANALGESIA

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Abstract

The aim of the present review is to discuss two interesting hypotheses that explain the pathophysiology of pain: (1) Arthur Craig's hypothesis that the experience of pain, elicited by specific sensors projecting into the central nervous system through afferent pathways, is relevant for homeostasis and represents a specific emotion related to a homeostatic behavioural drive; and (2) Wilfrid Jänig's hypothesis that, in functional chronic pain syndromes, specific changes occur in autonomic, endocrine and somatic motor systems interactions which, then, result in dysregulation involving peripheral, spinal and brain mechanisms. Theoretically, on the basis of these two hypotheses, hypnotic suggestions for analgesia can affect pain at multiple levels, including its generation at the periphery, secondary sensory neurons sensitization, and modulation of endocrine/immune responses through the modulation of autonomic activity.

Key words: analgesia, autonomic nervous system, homeostasis, pain

Introduction

Homeostasis is a dynamic process based on multiple integrated mechanisms that are responsible for the maintenance of the optimal physiological balance (Cannon, 1939). The behavioural state (sleep, arousal, wakefulness, attention, vigilance, circadian timing) consisting of intrinsic neural processes involving the whole brain activity determines which 'homeostatic' balance should be achieved. Cognitions and affective-emotional processes modulate and, sometimes, initiate 'homeostatic' behaviour.

All the specific information concerning the condition of the body and the physiological status of various tissues, essential for homeostatic balance, is conveyed to the spinal cord by small diameter (A delta and C) primary afferent fibres (Figure 1). A recent hypothesis (Craig, 2002; 2003a) suggests that pain should not be regarded as a submodality of cutaneous sensation or exteroception but as a homeostatic emotion, akin to temperature, itch, hunger and thirst, being both a specific sensation and a variable emotional state. For instance, there are similarities in homeostatic functions of thermoregulation and pain: first, both are processed together in the central nervous system, and secondly, non-painful thermal stimuli elicit an affective motivation, a sensation of pleasantness or unpleasantness that depends on the functional context associated with reflexive autonomic adjustments. The latter include, in all mammals, modulation of cardio respiratory activity as well as immediate and delayed behavioural modifications.

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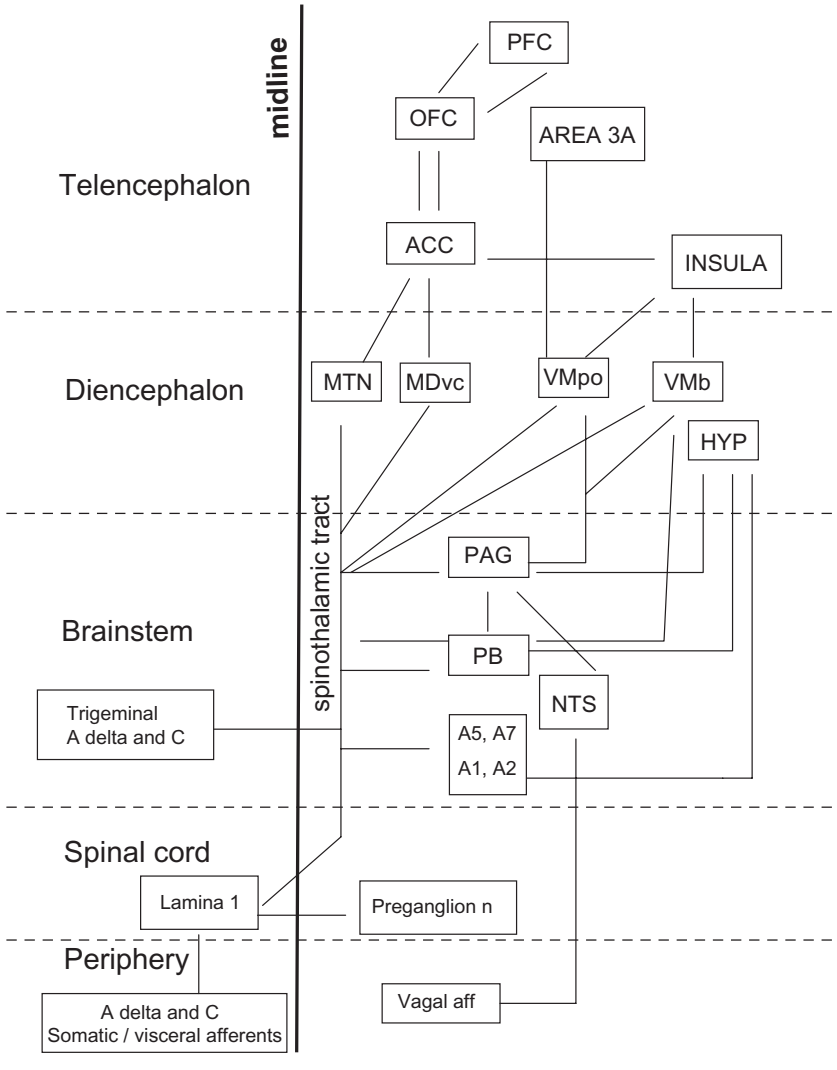

Figure 1. Schematic view of ascending afferent information to central structures. From the bottom: projection of lamina I neurons to sympathetic pre-ganglionic neurons to form a spino-spinal loop for somato-autonomic reflexes, and to pre-autonomic sites in the brain stem (catecholamine cells groups A1- A2 and A5 and A7), the parabrachial nucleus (PB) and the periaqueductal gray (PAG) that receive also information from visceral organs by the way of nucleus of tracti solitarii (NTS). The PB nucleus, the main integration site for all homeostatic afferent activity, densely projects to the PAG (the *mesencephalic homeostatic motor center*) and to the hypothalamus (HYP) (the *diencephalic homeostatic motor centre*) which organizes goal-directed autonomic, neuroendocrine and behavioural activity. In all mammals the homeostatic afferent information from the PB reaches the anterior cingular (ACC) and insular cortices by way of the medial thalamic nuclei (MTN) and basal ventral medial nucleus (VMb). Spinal and trigeminal lamina 1 neuron activity is mainly integrated at several brain stem sites, but is also projected to the controlateral thalamus via the lateral spinothalamic tract. This pathway, which appears in monkeys and is well developed in humans, projects to the posterior ventral medial nucleus (VMpo) which not only sends a corollary projection to area 3a in the sensory motor cortex, but, together with parvicellular ventroposteromedial nucleus (VMb), provides the topographic homeostatic afferent information to the dorsal posterior insular cortex (the interoceptive cortex). OFC: orbitofrontal cortex; PFC: prefrontal cortex; HYP: hypothalamus.

Contemp. Hypnosis 26: 4–14 (2009)
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It has been recently suggested (Watts and Swanson, 2002; Jänig, 2006) that the coordinate activation of the three divisions of the motor system – somatic, autonomic and neuroendocrine – are integrated with the sensory representations of the body and are responsible for the generation of behaviour. The integration occurs at three main levels, that is the spinal cord, the brain stem and the hypothalamus. This integration is hierarchically organized.

Homeostatic imbalance, and thus pain, elicits fast and slow defence responses. The former is characterized by increased vigilance, heart rate, blood pressure and limb blood flow, and is organized by the hypothalamo-mesencephalic and hypothalamus-pituitary-adrenal axis systems (Figure 2). These two mechanisms, activated by the medial prefrontal cortex, are responsible for integrative responses including non-opioid mediated analgesia and avoidance behaviour. They work through the synergic action of the dorsolateral and lateral columns of periacqueductal grey matter (PAG) of the mesencephalon and the sympathetic nervous system (Bandler, Price and Keay, 2000a; Bandler, Keay, Floyd and Price, 2000b). The latter – slow defence response – is characterized by recuperation and healing of tissues, quiescence, reduced heart rate and vasomotor activity due to parasympathetic prevalence, and by opioid mediated analgesia; the corresponding neural circuits originate in the orbital prefrontal cortex which activates the ventrolateral PAG. The two PAG systems have reciprocal connections and are responsible for several functions in the regulation of behaviour (beside the reaction to pain) through the activation of the ventromedial medulla and of the dorsolateral pontine tegmentum (Fields, Basbaum and Heinricher, 2006; Heinricher and Ingram, 2008). They are activated by peripheral nociceptors and can generate both hyper and hypoalgesia, according to the active and passive body coping strategies able to counteract the homeostatic unbalance elicited by psychological or physical stressors.

Hormone levels are modulated during the fast defence phase (fight or flight response) as well as during the slow recuperative activity and represent a relevant part of the response to pain together with the immune response, whose bidirectional functioning –

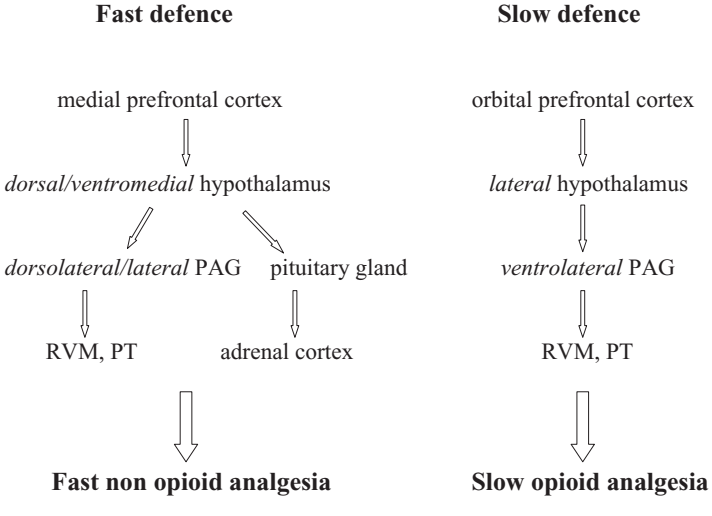

Figure 2. Brain structures involved in the mechanisms of analgesia. RVM: rostro-ventromedial medulla; PT: pontine tegment.

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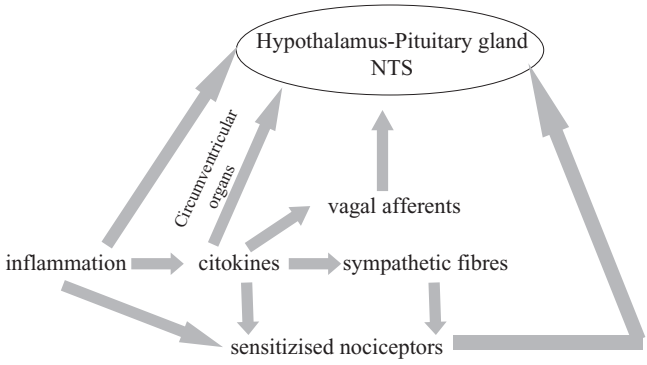

Figure 3. Interactions between endocrine-immune-autonomic systems in sensitization. NTS: nucleus tractus solitarii.

brain-immune system-brain – is modulated by both the autonomic and endocrine activity. The immune system can inform the defence systems in the brain by cytokines via the circumventricular organs, by vagal afferent neurons and nucleus tractus solitarii (Figure 3). The brain, in turn, modulates the reactivity of the immune system, primarily via the brain stem sympathetic control centres and the hypothalamo-pituitary system. Cytokines are involved in the sensitization of nociceptors during inflammation through their fast effect on the sympathetic terminals (*see* Watkins and Maier, 1999; Jänig and Levine, 2006) and through the slow changes of nociceptors sensitivity linked to the activation of the sympatho-adrenal system (Maier and Watkins, 1998; Watkins and Maier, 2000).

It is not clear whether or not the immune system affects the sympathetic nervous system via a specific sympathetic channel anatomically and functionally different from the sympathetic channels to other target cells (Besedovsky and del Rey, 1995; Hori, Katafuchi, Take, Shimizu and Niijima, 1995; Madden and Felten, 1995; Madden, Sanders and Felten, 1995; Schedlowski and Tewes, 1999; Ader, 2007;). However, in monkeys, chronic social stress enhances the sympathetic innervation of parenchymal areas of the lymph nodes containing T lymphocytes, but not the innervation of blood vessels in lymph nodes (Sloan, Capitanio, Tarara, Mendoza, Mason and Cole, 2007; Sloan, Capitanio and Cole, 2008).

A new role for the autonomic system

There is evidence that, in contrast with Cannon's original theory (Cannon, 1939), the sympathetic branch of the autonomic nervous system does not react as a unitary system (Jänig and Levine, 2006) and does not function antagonistically with respect to the parasympathetic branch (Berntson, Cacioppo and Quiqley, 1993). In addition, at present, autonomic visceral afferent neurons cannot be considered the only components of autonomic reflexes and regulations, since small diameter somatic afferents also contribute to somatic and visceral representation in the brain (Craig, 2002). The small diameter (A delta and C) primary afferent fibres are conveyed to the spinal cord and terminate monosynaptically on dorsal horn lamina I neurons, which originate from progenitors of sympathetic interneurons that migrate to the top of dorsal horn at the same time of the arrival of small diameter peripheral afferents and together they form a cohesive afferent system.

DOI: 10.1002/ch

Figure 1 shows the afferent pathways responsible for the homeostatic joint role of autonomic, somatomotor and endocrine systems.

There are neural asymmetries in homeostasis control. Indeed the hepatic nerve, which innervates the liver, is a branch of the left vagus nerve (Rogers and Hermann, 2005) and in humans its afferents terminate exclusively in the left brain stem (Craig, 2005). Moreover, heart rate control is predominantly a right-sided function while ventricular regulation and pulse pressure are predominantly left-sided functions (Oppenheimer, Gelb, Girvin and Hachinski, 1992). In humans, the ascending projections from parasympathetic and sympathetic afferents are modality-specific, topographically organized projections to the ventromedial nucleus of the thalamus and become lateralized as they project to higher-order homeostatic centres (Craig, 2002). A homeostatic model of emotional asymmetry has been recently proposed (Craig, 2005) in which the right forebrain is mainly associated with sympathetic activity – namely with arousal, pain, aversive behaviour, danger and survival emotions – while the left forebrain is associated with parasympathetic activity, i.e. with nourishment, positive affect, safety and appetitive behaviour.

In humans, the interoceptive information related to homeostatic and autonomic activity (pain, hunger, thirst, muscle exercise) is not associated with specific activity in the parietal somatosensory cortex, but with that of the insula which is reciprocally connected with ACC, amygdala, hypothalamus and orbitofrontal cortex (Figure 1). The insula plays a crucial role in the modulation of homeostatic functions and in the generation of motivations and emotions critical for survival needs. Indeed, insula and ACC activations provide the essential substrate for 'an image of the physical self as a feeling entity which is characteristic of human consciousness' (Craig, 2002), an idea consistent with the hypothesis that the sense of homeostatic condition provides information for the subjective image of the 'material me' (Damasio, 2003) and in line with the theory originally presented by William James (1884) linking viscero-afferent feedback to emotional experience. In particular, in humans the 'feeling itself' is engendered in the dorsal margin (the so-called interoceptive cortex) and in the anterior part of the insula, while the 'behavioural agent' is represented in the ACC (Craig, 2002).

The same brain areas have been shown to be activated in various pain-related conditions (subjective pain perception, pain anticipation, subjective reduction or generation of pain), and also by non-painful information, i.e. sensual touch, vehicolated by unmielinated afferent fibres projecting to lamina 1 neurons and then by a pathway common to pain and the other homeostatic information (Vallbo, Olausson and Wessberg, 1999; Olausson, Lamarre, Backlund, Morin, Wallin, Starck, Ekholm, Strigo, Worsley, Vallbo and Bushnell, 2002). This suggests how a particular individual state might modulate the experience of pain and, for instance, why severe pain is not necessarily always associated with a low subjective well-being (Huber, Suman, Biasi and Carli, 2008).

Also at the peripheral level, the convergence of painful and non-painful information allows associations between painful and non-painful information within one homeostatically relevant sensory system (Craig, 2002; 2003c). In fact, there are two different classes of lamina 1 neurons involved in the sensation of the first (sharp) and second (burning) pain, respectively. The neurons responsible for the second pain are mainly polymodal and receive monosynaptic input from C fibres related to noxious heat, pinch and cold (HPC), but they are responsible for burning pain also when simultaneously stimulated by innocuous cold and warm stimuli eliciting the grid illusion of pain. The perception of burning pain might depend on the integration of the thermal sensory modalities within the homeostatic, rather than within the nociceptive function. Indeed, these polymodal neurons display ongoing activity related to the metabolic needs of tissues that require

DOI: 10.1002/ch

longer lasting responses, as occurs during sickness behaviour associated with immune modulation.

Visceral pain is generated by activation of high threshold, normally silent, visceral thoracolumbar or sacral afferent neurons, with the contribution of low-threshold mechanosensitive afferents that encode both non-noxious and noxious intraluminal pressures and are sensitized during inflammation (Häbler, Jänig and Koltzenburg, 1993a; 1993b; White, Smithwick and Simeone, 1952; *see* Cervero and Jänig, 1992; Cervero 1994, 1996; Gebhart and Bielefeldt, 2008), probably due to an involvement of spinal autonomic non-vasoconstrictor pathways to visceral organs (Jänig, 2008a). Sensitization of visceral afferent neurons could lead to a sensitization of second-order neurons in the spinal dorsal horn and establish positive feedback loops between visceral afferent neurons, spinal autonomic systems and visceral effector organs. Nonetheless, visceral pain could be generated even in the absence of both visceral trauma and of visceral afferents' sensitization by changes affecting the supraspinal centres and the positive feedback loops between visceral organs and spinal cord (Jänig, 2008a; 2008b). Modulation of positive feedback loops between spinal autonomic systems, visceral organs and visceral afferent neurons might be critical to explain several functional diseases such as cardiac pain without ischemia, non-cardiac chest pain, pain in non-ulcer dyspepsia and pain in irritable bowel disease.

Models of sympathetic-afferent coupling

In physiological conditions, the efferent sympathetic systems and the afferent systems do not appear directly or indirectly coupled in peripheral tissues. In fact, healthy subjects show intimate interactions between vascular sympathetic afferents and mechanical insensitive fibres, but activation of catecholamine receptors in nociceptors does not generate excitation or mechanical sensitization. Indeed, catecholamines induce acute heat hyperalgesia, but not mechanical sensitization or mechanical hyperalgesia or axon reflex erythema.

During inflammation or following nerve lesion, the efferent (noradrenergic) innervation of the affected tissue may feed back to the primary afferent neurons and activate them or enhance their activity, leading to a pain syndrome, typically affecting limbs, called sympathetically maintained pain (SMP). SMP is a systemic disease involving the central and peripheral nervous system associated with changes in somatic sensations, i.e. increase of detection thresholds for mechanical, cold/warm/heat stimuli. In this syndrome, there is pain relief by sympathetic block, exacerbation of pain by application of norepinephrine (NE) in painful skin areas, increase in pain by sympathetic arousal, but no evidence of increased sympathetic outflow, no increase in reflex sympathetic vasoconstrictor response, and no increase in venous concentration of NE in the affected limb. In SMP patients, NE does not activate polymodal nociceptors but silent, mechanical insensitive nociceptors (Jørum, Ørstavik, Schmidt, Namer, Carr, Kvarstein, Hilliges, Handwerker, Torebjork and Smelz, 2007). The cross talk between sympathetic postganglionic fibres and afferent neurons occurring in peripheral tissues is mediated by NE and alpha-adrenoceptors in the afferent neurons (Jänig, 2008a, 2008b) or obtained, indirectly, via the vascular constriction (generated by vasoconstrictor neurons) and the ensuing changes in the affected tissue. Also adrenaline, released by the adrenal medulla and representing the endocrine efferent component of sympathetic activation, may sensitize nociceptors to mechanical stimulation, as shown by experiments on prolonged exposure of nociceptive afferents to increased plasmatic adrenaline concentrations (Khasar, Miao,

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Janig and Levine 1998a; 1998b; Khasar, Miao, Jänig and Levine, 2003). It has been shown in experimental rat models that the sympathetic activity is also responsible for the sensitizing effects of nerve growth factor on nociceptive afferents possibly via trkA receptors (McMahon 1996; Woolf, 1996) or via the cytokine interleukin 8 (IL-8) release (Woolf, Ma, Allchorne and Poole, 1996; Poole and Woolf, 1999).

As a general rule, the alteration of body loops involving the autonomic pathways might be critical for the development of chronic pain disorders (Jänig, 2008b). In fact, chronic pain syndromes are characterized by changes in autonomic target cells depending on the changes of ongoing and reflex activity in neurons of the peripheral autonomic pathways. This, in turn, is modulated by changes in central autonomic structures and by the neuroendocrine system. Thus, centrally generated autonomic modifications elicit parallel changes in body perception through the connection between the efferent autonomic terminals, their target cells and the peripheral afferents responsible for central representation of body maps, endocrine functions and the somatomotor system. In generalized chronic pain syndromes, a sensory-motor mismatch related to alteration in autonomic efferent-body tissue afferent loops, which lose their precise temporal and spatial coordination, might account for the sensory-affective, autonomic, motor and endocrine abnormalities (Jänig, 2008b).

Conclusion

The general perspective indicated by the above findings considers pain as a multifaceted physiological state including a specific sensation, a variable emotional state, an aspect of interoception and a specific behavioural motivation (Craig, 2002; 2003a; 2003b). Neuroimaging studies (Critchley, Wiens, Rotshtein, Ohman and Dolan, 2004; Pollatos, Schandry, Auer and Kaufmann, 2007) show that the autonomic activity is monitored in cerebral areas contributing to the development and maintenance of the representations of body domains in the brain as well as to the construction of the experience. Changes in the activity of the autonomic pathways affect the activity of small afferent fibres innervating body tissues, which elicit modifications in the corresponding body maps. Modulation of the interaction between the loops connecting the autonomic control systems involved in emotions, with the neural systems responsible for body maps represent the basis for body sensations and emotional feelings in healthy subjects (Damasio, 1999; 2003; Critchley, Mathias, Josephs, O'Doherty, Zanini, Devar, Cipollotti, Shallice and Dolan, 2003; Critchley et al., 2004; Jänig, 2006; Pollatos et al., 2007). In the same vein, in functional chronic pain syndromes, pain symptoms are correlated with changes involving the autonomic nervous system, endocrine systems and the somatomotor system and are the result of a central dysregulation involving mechanisms in the spinal cord, brain stem and forebrain (Jänig, 2008a).

The central control of pain perception by hypnotic suggestions (Rainville, Duncan, Price, Carrier and Bushnell, 1997; Faymonville, Roediger, Del Fiore, Delguedre, Phillips, Lamy, Luxe, Maquet and Laureys, 2003) as well as by instructions for analgesia administered to not hypnotized patients (Derbyshire, Whalley and Oakley, 2008) is a well-documented phenomenon. The physiological findings discussed in the present review allow hypothesizing that, theoretically, hypnotic suggestions for analgesia can influence also pain generation, secondary sensory neurons sensitization and modulation of endocrine/immune responses associated with pain through the modulation of the sympathetic activity.

DOI: 10.1002/ch

Although the hypnotic treatment is effective also in low hypnotizable patients (Jensen and Patterson, 2006), probably due to enhancement of their placebo responsiveness (Carli, Suman, Biasi, Marcolongo and Santarcangelo, 2008), the high flexibility in autonomic control exhibited by the subjects highly susceptible to hypnosis (see Sebastiani, D'Alessandro, Menicucci, Ghelarducci and Santarcangelo, 2007) represents an even more powerful tool for pain control. In addition, the low vulnerability to the autonomic effects induced by pain and stress observed in these subjects (Santarcangelo and Sebastiani, 2004; Jambrik, Carli, Rudish, Varga, Forster and Santarcangelo, 2005; Balocchi, Varanini, Menicucci, Santarcangelo, Migliorini, Fontani and Carli, 2005) might be a further advantage (Carli, Huber and Santarcangelo, 2008). In fact, the central monitoring of the autonomic activity is relevant in the construction of the '*self*' (Damasio, 2003) and changes in the activity of the autonomic nervous system might induce a reinterpretation of physical sensations by changes in the central representation of the *self.*

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