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Commentary

Pain relief from deep brain stimulation at midbrain sites — A contribution from vagal processes?

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Some 4 decades ago the extraordinary report of analgesia evoked by midbrain stimulation in conscious rats (Reynolds, 1969) triggered a sea change in our understanding of the pain process. The identification of specific pathways originating from the midbrain periaqueductal grey matter (PAG), which could modulate the transmission of nociceptive information at the level of the dorsal horn provided an anatomical basis for the clinical observation famously first put on record by Beecher (1946) that pain sensation was not a fixed entity but modifiable by affect. It soon became clear that the newly discovered pain control system originating in the PAG was in fact composed of several parallel descending control systems dedicated to enhancing or inhibiting nociceptive transmission at the level of the spinal and trigeminal dorsal horns and with a complex pharmacology (Gebhart, 2004). These control systems appear to be in a state of dynamic balance. Under resting conditions i.e. no pain, ongoing activity is present in both inhibitory and facilitatory systems with the balance tipped slightly towards facilitation (Bee and Dickenson, 2007). Stimulation of nociceptors changes this relationship. The onset of tissue injury triggers a 3-stage process that commences with engagement of descending inhibitory mechanisms. The ensuing elevation in nociceptive thresholds is part of a panoply of adaptive behaviours and physiological responses activated by the "stress" or "danger" of the situation, as well as the signalling of actual or impending tissue damage. In this way the risk of pain compromising motor performance is minimized, allowing the organism to escape the injury-causing event (e.g. an attack). In other words, pain or the threat of pain triggers an initial adaptive response to promote survival (Lovick, 1993; Millan, 2002). After the acute danger has passed, the pain regulatory system shifts to a relative predominance of descending facilitation, with pain now acting as a signal to avoid further injury and to promote behavioural patterns that allow healing (Millan, 2002). If pain persists beyond this initial healing period, descending inhibitory pathways display progressively increasing activity to facilitate the resumption of normal activities required for long-term survival (Millan, 2002).

The ability to harness the pain inhibitory pathways to therapeutic advantage is the goal of neurosurgeons performing deep brain stimulation (DBS) procedures for relief of pain. High levels of success were claimed in the earliest studies (Hosobuchi et al., 1977; Young and Brechner, 1986). Others however, emphasized the incidence of aversive side effects (Nashold et al., 1969; Kumar et al, 1997) and the popularity of the procedure declined. However, DBS is once again being used very effectively by specialist centres to provide pain relief for appropriately selected patients, who are refractory to pharmacotherapy. Interestingly, relief from pain is often accompanied by cardiovascular changes (Green et al., 2006) suggesting that in humans, as has been demonstrated in animal models (Lovick, 1985, 1993), control of pain and autonomic responsiveness are inextricably linked.

Somato-autonomic links in control of pain responsiveness

Pain may be viewed as an example of a homeostatic response (Craig 2003), reflecting an adverse condition in the body that requires a behavioural response underpinned by autonomic adjustments. By way of example to illustrate the crucial service role of the autonomic nervous system in underpinning adaptive behaviour, food seeking behaviour would be pointless without the accompanying finely orchestrated sequence of smooth muscle and glandular events in the gastrointestinal tract. The ability of mammals to thrive in a broad range of climatic conditions is dependent on highly efficient autonomically driven mechanisms that regulate core body temperature within a narrow range.

In terms of pain, a neuroanatomical substrate for somato-autonomic integration has been revealed by studies on the descending control systems emanating from the midbrain PAG. Antinociception evoked by activation of neurones in the dorsal region of the PAG, an area which also elicits positive engagement with the environment (active coping in animal models) was accompanied by intense sympathoactivation and a pattern of autonomic adjustment that

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characterized defensive behaviour (Lovick, 1985, 1993; Bandler et al., 2000). Thus blood pressure and heart rate rose, respiration increased and the raised cardiac output was diverted to skeletal muscle. In contrast, hypoalgesia evoked from stimulation at ventral sites, which is associated with quiescence and withdrawal from the environment, was accompanied by a different pattern of autonomic response characterized by falling blood pressure and heart rate (Bandler et al., 2000). Furthermore, the dorsally evoked autonomic changes are predominantly sympathoexcitatory, whilst autonomic adjustments evoked from more ventral sites in the PAG involve vagal parasympathetic activation (Haxhiu et al 2002; Inui et al, 1994; Subramanian et al., 2008).

Vagal activity, emotionality and HRV

The vagus nerve is the main effector of parasympathetic autonomic control of the heart and almost all internal organs. The rate at which the heart beats is determined by activity in the vagus, which slows heart rate, and the sympathetic nerves, which accelerate it. Heart rate, measured as beat-to-beat intervals between the R-wave of the electrocardiogram (ECG), is not constant and varies with time. Heart rate variability (HRV) determined from R–R intervals can be used as an index of vagal activity. In the time domain the standard deviation of R–R intervals (SDNN), the root mean square of successive differences (RMSSD), together with measures of baroreflex sensitivity (an index of the responsiveness of the cardiovascular system to changes in blood pressure) have been shown to be useful indices of vagal activity. In recent times, power spectral analysis in the frequency domain has become the more commonly used measure. Power spectral analysis of R–R intervals of the ECG reveals the presence of both low frequency (LF: 0.04–0.15 Hz) and high frequency (HF: 0.15–0.40 Hz) spectral powers. The HF power has been shown to reflect primarily parasympathetic influences linked to the respiratory rhythm (sinus arrhythmia). LF power may also reflect parasympathetic activity but also indicates the extent of sympathetic influences (Parati et al, 1995), although the relative contributions continues to be a matter of debate.

The ease of recording the ECG and the ready availability of commercially available software analysis packages has tempted clinicians and scientists alike into the arena of HRV measurement. Studies of its control of the heart have revealed a close link between vagal nerve activity, as reflected by HRV, and emotional status. There is now an overwhelming consensus that healthy cardiac activity involves a high degree of beat-to-beat variability, which provides a protective effect against myocardial infarction and heart failure, especially in patients with existing cardiac disease (Huikuri et al, 2009). An association of low total spectral power in the HRV signal with death and disability related to other pathophysiological states such as diabetes, obesity, smoking and high cholesterol has also been recognised (Thayer et al, 2010a) suggesting that HRV may serve as a prognostic indicator for health in general. It could also serve as a tangible readout concerning the ability of the nervous system to organize an affective homeostatic response in accordance with the situational demands placed upon it.

In support of this idea several recent studies have reported an association between negative affect and low HRV. In a recent meta analysis of studies on depressed patients Kemp et al (2010) concluded that depression is associated with reduced HRV and that individuals with more severe depression are likely to have lower HRV than those with milder symptoms. In another study on apparently healthy individuals, low HRV was predictive of impaired recovery of cardiovascular, endocrine, and immune markers following a mental stress test (Weber et al 2010). Susceptibility to a stressful working environment is another factor associated with low HRV (Thayer et al, 2010b). Interestingly, in such subjects mood enhancing lifestyle changes such as physical exercise and active stress management can restore HRV levels to normality (Thayer and Lane, 2007; Tracey 2007).

Far less is known about the relationship between HRV and pain. However, low amplitude HRV in the high frequency domain has been shown to correlate with increased sensitivity to pain (Appelhans and Luecken, 2008). The recent study by Pereira et al. published in this journal (Exp Neurol 2010 223, 574–581) takes this finding further. In Pereira and colleagues' study in chronic pain patients HRV was monitored whilst using deep brain stimulation at dorsal or ventral sites in the PAG to activate descending pain control pathways to alleviate pain. Stimulation at all sites produced a reduction in pain scores but ventrally placed electrodes also elicited an increase in high frequency power of the HRV spectrum. Whilst there are some reservations regarding the study, particularly the failure to control for the effects of changes in respiratory pattern evoked by PAG stimulation, which could influence the HRV signal (Aysin and Aysin, 2006), the findings are important because they highlight the ventral PAG as a co-ordinating centre for emotional and somatosensory components of pain in humans. Changes in HRV coincident with pain relief do not by themselves indicate a causal link. However, the fact that only the pain relief from ventral stimulation sites was accompanied by increased HRV suggests it is likely to have been a direct effect of the stimulation rather than a form of emotional "relief" response secondary to the reduction in pain. Interestingly, sensations of pleasurable well-being, to which vagal activity may be linked, have been reported by others during DBS in the rostral periventricular grey for intractable pain (Kumar et al., 1997; Young 1989).

Pereira and colleagues' patients represent a highly selected group. The failure to respond to conventional analgesic pharmacotherapy, yet their responsiveness to DBS, may give an important clue to the nature of their pain. In recent years it has been recognised that neuropathic pain is associated with disturbed immune function not only peripherally in the form of inflammation around the site of injury but also centrally, where it is reflected by glial cell activation. One of the exciting implications to arise from the findings reported by Pereira et al., 2010 is the possibility that they may have uncovered a source of central control of brain immune function.

Vagus and immune function

An intriguing picture is emerging linking chronic pain, immune function and vagal nerve activity. Compelling evidence now exists for a suppressant effect on the immune system mediated via the vagus. Vagal signals to the spleen are key to this effect and have been shown to regulate leukocyte trafficking to peripheral inflammatory sites by controlling neutrophil surface CD11b levels (Huston et al, 2009). The mechanism is dependent on the a7 subunit of the nicotinic acetylcholine receptor, which inhibits NF-kB nuclear translocation and suppresses cytokine release by monocytes and macrophages (Huston et al., 2006; Rosas-Ballina and Tracey, 2009). This effect of vagal stimulation is extremely powerful. In mice vagal stimulation-induced attenuation of endotoxin-induced TNF (tumour necrosis factor) persisted 48 h after the stimulation ceased (Huston et al., 2007). Even in healthy human subjects HRV (an index of cardiac vagal function) was inversely related to inflammatory markers (Haensel et al 2008) and decreased HRV was independently associated with elevated plasma IL-6 (inflammatory cytokine) levels (von Känel et al., 2008). In addition to signalling information on physiological aspects of visceral status vagal afferents can be activated by pro-inflammatory cytokines such as IL-1β in damaged tissue (Goehler et al., 2000). At the centre of this neuro-immune reflex pathway (Tracey, 2002), the PAG, which receives widespread inputs from internal organs via the vagus (Viltart et al, 2006), is in an ideal position to detect immune-related events in the periphery and initiate appropriate homeostatic autonomic and behavioural responses to counteract the disruptive effects of pain. It is not known whether HRV, which so far has been demonstrated to relate only to cardiac function, can be generalised

to all vagal efferent activity. If it can, then activation of the immune suppressing pathway in chronic pain patients using DBS to engage vagal influences, could contribute to relief from their pain.

Whilst the peripheral release of immunoactive substances such as cytokines, neurotrophic factors, and chemokines initiates local actions, it can also result in a more generalised immune response within the central nervous system. The neuroinflammatory mediators can gain access to the brain and spinal cord through weak spots in the blood brain barrier or via sensory nerves and trigger activation of glial cells located in the spinal cord and the brain. Activated glia play a prominent role in nociception by triggering a cascade of events leading to prolonged release of a host of pro-nociceptive substances. These act to enhance the development of the long-term potentiation-like mechanisms that underpin the development of sustained activity in ascending pain pathways in chronic neuropathic pain states (Vallejo et al, 2010). Whether vagal activation can influence these central effects directly is currently unknown.

In specialist hands deep brain stimulation for pain relief is proving a powerful tool for the management of pain in a selected patient population. An added bonus is that the procedure is yielding new information regarding the mechanisms underlying the pain process. This is perhaps the importance of the work being carried out by Pereira and colleagues in Oxford who, by looking beyond the immediate goal of pain relief, have generated data that may have important implications for refining and developing existing techniques and pain management strategies.

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