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Relationship Between Blood- and Cerebrospinal Fluid–Bound Neurotransmitter Concentrations and Conditioned Pain Modulation in Pain-Free and Chronic Pain Subjects

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Abstract: **Descending pain inhibition is an endogenous pain control system thought to depend partially on the activation of bulbospinal monoaminergic pathways. Deficits in descending pain inhibition have been reported in numerous human chronic pain conditions, but there is currently no consensus regarding the neurochemical correlates responsible for this deficit. The aims of this study were to 1) assess the efficacy of descending pain inhibition in pain-free and chronic pain subjects, 2) screen for changes in centrally (ie, cerebrospinal fluid) and peripherally (ie, plasma) acting monoamine concentrations, and 3) explore the relationship between descending pain inhibition and monoamine neurotransmitter concentrations. Our results clearly show a deficit in pain inhibition, along with lower plasma norepinephrine and metanephrine concentrations in chronic pain subjects, compared to pain-free subjects. No differences were found in cerebrospinal fluid neurotransmitter concentrations. Finally, our results revealed a positive relationship between blood-bound norepinephrine and metanephrine concentrations and the efficacy of descending pain inhibition. Thus, basal monoamine levels in blood were related to descending pain inhibition. This finding supports the emerging idea that individual differences in descending pain inhibition may be linked to individual differences in peripheral processes, such as monoamines release in blood, which are possibly related to cardiovascular control.**

Perspectives: ***This article presents psychophysical and neurochemical findings that indicate that the latent potential of descending pain inhibitory responses is associated with differential activity in peripheral processes governed by monoamine neurotransmitter release, bringing insights into the relationship between descending pain inhibition and cardiovascular control in humans.***

Key words: *Descending pain inhibition, monoamines, mass spectrometry, plasma, blood pressure.*

Preventing and treating chronic pain (CP) continues to be a vexing challenge for health care professionals—largely because we have a limited understanding of the pathophysiological processes involved. Despite evidence of peripheral and central sensitization in many CP conditions, the literature is beginning to show that impaired endogenous pain modulation is a common, yet clinically underappreciated characteristic of CP.[18,26,35] A growing number of studies indicate that deficient endogenous pain modulation may be a pathognomonic sign of CP.[3,6,7,10,22-24,27,30,33,45]

Descending pain inhibition, an endogenous form of pain control, can be triggered through either direct or indirect activation of midbrain (eg, periaqueductal gray) and medullary (eg, rostro-ventromedial medulla) structures. Activation of these brain structures leads to a widespread inhibition of spinal nociceptive signals, notably via the recruitment of descending monoaminergic pathways, including those that release norepinephrine (NE) and serotonin (5-HT). Targeting NE and 5-HT monoaminergic systems, therefore, may be important

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when seeking to better understand the link between descending pain inhibition and CP and when exploring new medical treatments for CP.[18,20,21,25,26,29] The proven pain-relieving properties of dual-acting 5-HT and NE reuptake inhibitors support the idea that descending pain inhibitory pathways are perhaps being disrupted in various CP states. A recent review even indicates that 5-HT and NE reuptake inhibitors are particularly effective at relieving neuropathic pain, fibromyalgia, and chronic low back pain.[42] Likewise, Yarnitsky et al recently demonstrated that duloxetine, a well-balanced 5-HT and NE reuptake inhibitor, was effective at relieving painful diabetic neuropathy when pretreatment levels of descending pain inhibition were modest. In other words, patients with a lower ability to inhibit pain had greater benefits from taking duloxetine.[44]

In the laboratory, descending pain inhibition can be triggered and studied using conditioned pain modulation (CPM) paradigms, such as those involving the cold pressor test (CPT).[31,39,43,45] These paradigms provide useful psychophysical information but do not provide information regarding the molecules responsible for ensuring strong descending pain inhibition. To this end, a direct quantification of 5-HT and NE content in cerebrospinal fluid (CSF) and in blood would provide valuable information on monoaminergic activity. To our knowledge, no study has ever quantified and compared CSF and blood monoamine levels among pain-free (PF) and CP subjects and explored the relationship between the concentration of these molecules and the strength of descending pain inhibition.

Our study will 1) measure descending pain inhibition using the CPT among PF and CP subjects, 2) quantify CSF and blood plasma monoamine neurotransmitter concentrations, and finally, 3) study the relationship between CPM and neurotransmitter levels. We hypothesize that, compared to PF subjects, CP subjects will have both weaker descending pain inhibition and lower monoamine concentrations, especially in the CSF. We further expect that CSF, but not blood, monoamine concentrations will be closely related to CPM efficacy (in all subjects).

Methods

Participants

Twenty male subjects who were prescheduled for a transurethral resection of the prostate (TURP) were recruited from the preoperative assessment clinic of the Centre hospitalier universitaire de Sherbrooke (CHUS). TURP is the surgical gold standard treatment for benign prostatic hyperplasia, a condition usually accompanied by painless lower urinary tract symptoms. TURP is performed under spinal anesthesia and, therefore, CSF sampling was possible during the procedure. Patients suffering from a malignant cancer, a central nervous system pathology, or any other condition capable of altering pain sensitivity were excluded from the study. Informed consent was obtained from all participants, and the study was approved by the institutional review board of the clinical research center of the CHUS (protocol ID 11-016).

Psychophysical pain testing was performed 3 to 5 days prior to surgery in our human pain laboratory at the clinical research center of the CHUS. Information regarding medical history was obtained following a semistructured interview. Participants were also asked to complete the State-Trait Anxiety Inventory,[34] the Beck Depression Inventory,[1] and the Pain Catastrophizing Scale[37] in order to create a psychological profile. Subjects were divided into 2 experimental groups (PF and CP) depending on the presence or absence of CP (defined as pain lasting more than 3 months). It is important to note that for all subjects included in the CP group, clinical pain was unrelated to benign prostatic hyperplasia. Subjects in the CP group had to additionally complete the Brief Pain Inventory.[9] For all participants, medical records were reviewed to confirm the presence of any and all previous diagnoses related to CP.

Pain Testing Procedure

Descending pain inhibition was triggered using a CPT, whereas the effects of inhibition on pain were measured using a tonic heat pulse (as previously recommended by Tousignant-Laflamme et al[39]). It is worth noting that when seeking to trigger descending pain inhibition, cold pressor pain is one of the most frequently used procedures.[31,39]

Pain Perception and Preexperimental Testing Phase

In this study, experimental pain consisted of a thermal heat stimulus provided using a 9-cm^2 Peltier thermode on the volar aspect of the right forearm of all participants. The thermode consisted of a heating plate connected to a computer, allowing for precise temperature control (TSA II; Medoc Advanced Medical Systems, Ramat Yishai, Israel). In the pretesting phase of the experiment, thermode temperature was set at 32°C and programmed to gradually increase at a rate of .3°C per second. Subjects were instructed to verbally report when their perception changed from nonpainful heat to painful heat (ie, thermal pain sensitivity [TPS]) and when their pain became intolerable (ie, thermal pain tolerance [TPT]). Participants used a computerized visual analog scale (CoVAS; ranging from 0 [no pain] to 100 [most intense pain that could be tolerated]) to evaluate their subjective experience of pain intensity. The temperature value corresponding to the temperature necessary to induce a 50/100 pain intensity was also recorded. This value, determined for each subject, represented the target temperature used during the testing phase of the experiment. For all subjects, the procedure was repeated 3 times to ensure response reliability.

Experimental Testing Phase

Using the thermode, tonic experimental heat pain (used to measure CPT-induced inhibition) was applied