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Introducing descending control of nociception: a measure of diffuse noxious inhibitory controls in conscious animals

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Introduction

Ever since Le Bars and colleagues detailed in 1979 that ‘’the activity of convergent dorsal horn neurons could be powerfully inhibited by noxious stimuli applied to various parts of the body’’ (21), diffuse noxious inhibitory controls (DNIC) have provided basic research a proxy measure of the functionality of a unique descending inhibitory pathway. This *pain inhibits pain*-like phenomenon was originally described in anaesthetised rodents, where it is possible to quantify functional DNIC as a decrease in the peripherally-evoked activity of spinal convergent neurons following application of a conditioning stimulus (CS) (2, 21). Interestingly, such naturally occurring analgesia upon conditioning is also observed in conscious humans (13, 22, 33). Conditioned pain modulation (CPM) is now used to describe the human counterpart of DNIC (35), and CPM paradigms are purported to assess the efficacy of DNIC as a surrogate measure of a descending inhibitory system (9).

Since the translational value of DNIC to CPM may be gauged by the predictive quality of human CPM processing, it is unsurprising that a focus on measuring the expression status of conditioning-activated descending inhibitory controls in behaving animals is coming to the fore (11, 12, 32, 37). An increasing number of human and animal DNIC and CPM studies (Fig. 1) highlights the timely need for consideration of what the appropriate terminology is when describing this effect. In recognition of the

fact that only DNIC-like behaviours can so far be measured in wakeful animals, and that it is not appropriate to use CPM to refer to a reduction in pain-related behaviours in pre-clinical research since animal responses are non-verbal, we recommend that the experimental quantification of descending modulatory pathway activation upon conditioning in wakeful animals be referred to as *descending control of nociception* (DCN).

Ensuring that the correct mechanism is cited when considering DNIC versus DCN versus CPM system execution in rodent and human studies is vital. While DNIC expression is maintained under rodent anaesthetic, CPM is measured in wakeful subjects and is thus representative of a complex cognitive input-influenced process. Mechanistically both are activated upon conditioning, but the unconscious processing of neuronal inhibition evidenced during DNIC cannot be assessed during CPM testing, and even though functional CPM likely involves activation of the DNIC pathway it also encompasses a higher cortical centre top-down modulatory circuitry that is influenced by personal attributes. In that vein, when measuring the inhibitory effect of conditioning in behaving animals, it is not only the expression status of the DNIC pathway that is being recorded. Rather now, a DCN effect must also represent a mechanism that encompasses attention to the potentially most damaging insult.

The DCN terminology would allow researchers to acknowledge a clear distinction regarding the subject's conscious state, where measurement of a functional DNIC response in anaesthetised versus wakeful animals evidently portrays execution of distinct top-down modulatory processes, while also accounting for potential variability in modulatory direction. In addition, an appropriately separate definition would more accurately enable preclinical and clinical DNIC, DCN and CPM comparators in back and forward translational studies.

Key considerations: The unconscious versus conscious state

When mechanistically interrogated in anaesthetised animals, DNIC expression, explicitly referring to the inhibition of wide dynamic range (WDR) neurons upon conditioning, represents the activation of a supra-spinal brainstem nucleus that projects directly to the dorsal horn of the spinal cord (1, 2). In behaving, conscious animals DNIC terminology is applied when quantifying changes in resting nociceptive responses to evoked stimuli (i.e. Randall-Selitto pressure stimulus, von Frey filaments, Hargreaves heat withdrawal threshold) upon injection of an irritant (i.e. capsaicin, formalin) to a distant body region (11, 12, 32, 37) despite the fact that direct spinal neuronal recordings are not made.

DNIC are abolished in rats following spinalisation (14) or cervical block with lidocaine (6), and a lesion to the dorsolateral funiculus (DLF) ipsilateral to an electrophysiologically recorded WDR neuron was previously shown to abolish DNIC expression (34). This suggests that the descending fibres responsible for functional DNIC expression likely travel via the ipsilateral DLF. It is noteworthy that, in wakeful animals, a DLF lesion (including a bilateral lesion) did not abolish hypoalgesia triggered by formalin (CS) injection, suggesting that additional tracts are involved in DNIC expression in behaving rats. Pertinently this highlights the complexity of defining a functional DNIC circuit in wakeful animals where the involvement of other parallel descending tracts is likely (7, 26).

Since it is measured in wakeful humans, CPM represents a complex process whereby cognitive inputs influence top-down sensory processing, including the expression status of inhibitory controls. Unlike DNIC as measured in anaesthetised animals,

'conscious' CPM can evoke pain-inhibitory or faciliatory effects, depending on the context (10, 16, 20, 24, 27, 36). This contextual (cues prone) aspect of CPM likely represents the involvement of at least two opposite neuronal systems. It also suggests that inhibition is a dominant component of unconscious processing that may involve, for example, counterirritation. On that, counterirritation was another term coined to describe a *pain inhibits pain*-like phenomenon, however its mechanistic meaning is less precise since it is not limited to the activation and function of descending inhibitory controls (8, 15, 18). Overwhelmingly, the heterogeneous nature of CPM outputs in the healthy population (10, 16, 20, 23) points to the complexity of the CPM system as compared to the direct functionality of DNIC when quantifying their expression statuses upon conditioning. Having a direct physiological measure of the functionality of an endogenous descending brain to spinal cord pain inhibitory pathway that is independent of an individual's subjective judgment would be the optimal way to truly denote what is, and who possesses, a 'net CPM' effect.

DNIC, DCN and CPM comparators

How comparable are the DNIC, DCN and CPM phenomena and why is it not appropriate to refer to their functionality interchangeably? Clearly, mechanistically speaking, measurement of a functional DNIC response in anaesthetised versus wakeful animals portrays execution of distinct descending processes where distraction from the sensation evoked by a test stimulus upon conditioning is predicted to be elicited as a minimum. In turn, those descending processes activated in behaving animals will not mirror those associated with a final net CPM effect when

acknowledging that wakeful animals do not quantifiably experience human emotions relating to, for example, the *monday blues* or divorce.

In humans cervical spinal cord transection (33) or medullary retro-olive lesions (Wallenberg's syndrome) diminishes CPM expression (13). It is noteworthy that the potential origin of DNIC to pontine nuclei (5, 34) corresponds exactly to the Wallenberg's syndrome-related lesions (4). Human CPM studies pinpoint upper brainstem (19) and cortical (3, 25) brain regions as impacting individual differences in terms of a pain-inhibiting response to a CPM paradigm, where modulatory roles are proposed. Due to the low spatial resolution of fMRI, assigning direct discreet pontine nuclei to CPM expression is so far not possible. Therefore, the precise definition of CPM 'effector' brainstem structures remains to be elucidated. Ideally, they will be defined in animal models such that physiological and pharmacological studies from rodents may be forward translated to humans.

Many studies have successfully studied the underlying functionality of CPM and DNIC paradigms in experimental conditions. Noradrenergic mechanisms explain the beneficial use of monoaminergic manipulation in analgesic therapies in terms of CPM functionality (29, 31, 36) in a manner that back translates (1, 2) and DNIC and CPM deficiencies are evident in varied chronicities (17, 22, 34).

CPM measurements are made in awake humans with the explicit understanding that conscious processing of top-down sensory modulation will impact the final expression status of descending control pathways (that very likely include DNIC). DCN terminology would allow a clear delineation regarding the mechanistic foundation of the effect observed, even when acknowledging that the full circuitry remains equivocal. A role for opioidergic transmisison in the anterior cingulate cortex

(ACC) in the modulation of DCN expression was recently shown in an animal behavioural model (28). ACC-mediated modulation of DNIC-pathway functionality potentially occurs via a relay in the periaqueductal grey (PAG), as suggested by earlier human functional studies (19), but animal lesion experiments do not support a crucial role for the PAG in DNIC expression (22). However this does not discredit a potential modulatory role in conscious animals, for example upon measurement of DCN. Confirmation of supra-pontine regulation of DCN (i.e. ACC, PAG) in conscious animals requires further investigation. Do CPM and/or DCN expression reflect DNIC pathway functionality and/or a strong (negative or positive) cognitive experience? DCN modulation by forebrain mechanisms is likely (30) and, even when recorded in anaesthetised rodents, the functional expression of DNIC is influenced by subcortical brain regions associated with emotional processing (32).

Thanks to precise genetically encoded tools (i.e. defined discreet neuronal population-targeted optogenetics), the anatomical and physiological definition of the DNIC origin nucleus is likely to soon be resolved. With this in mind, inhibitory/facilitatory control of the DNIC origin nucleus in behaving wakeful animals is on the immediate research horizon. Therefore, a precise terminology that accurately reflects animal behavioural responses upon its eventual manipulation is imperative.

Concluding

We propose that a distinction between DNIC and CPM should be made in animal studies based on the subject's conscious state (where, interestingly, the conscious state appears to be a source of variability in rodent studies as with human CPM studies). The fact that DNIC are expressed in anaesthetised, unconscious animals

highlights its autonomous circuitry. DNIC expression may be modulated in wakeful states by cortical influences, and as such resembles CPM. Using common, precise definitions for DNIC, CPM and DCN phenomena avoids confusion regarding that fact that CPM and DCN may involve DNIC mechanisms, but not the other way around.

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FIGURE LEGEND

Figure 1. The number of DNIC (diffuse noxious inhibitory control) animal, DNIC human, CPM (conditioned pain modulation) animal and CPM human publications according to the timelines indicated. Based on a pragmatic PubMed search (timeline results by year) performed November 2020.