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Clinical correlates of Stress-induced Analgesia: Evidence from Pharmacological Studies

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1. Introduction

Exposure to aversive stimuli or contexts results in profound analgesia. Beecher and colleagues [3] observed that World War II soldiers suffering from battle wounds often experienced little pain, whereas similar injuries in a non-threatening environment would be perceived as highly painful. These initial observations gave rise to the concept that the perception of pain is heavily influenced by context. The development of well-characterised, animal models of analgesia associated with aversion (unconditioned or conditioned stress-induced analgesia (SIA)), provided the first opportunity to study the neurobiological mechanisms underpinning this evolutionarily significant phenomenon. Clinical studies of SIA have substantiated evidence from animal studies and enhanced our knowledge of this phenomenon in humans. An increased understanding of the neurobiological mechanisms underpinning this extremely potent form of endogenous analgesia is of both fundamental physiological importance and potential therapeutic significance. Here we provide a brief initial overview and update of preclinical studies of SIA and then examine the extent to which the pharmacological mechanisms identified also apply in humans.

2. Animal models of stress-induced analgesia (SIA)

Animal models of SIA typically combine an unconditioned or conditioned stressor with a test for nociceptive behaviour. SIA can be induced in laboratory animals during or following exposure to unconditioned physical stressors such as inescapable electric footshock, forced swimming, or thermal hot-plate stress [2]. Analgesia is also expressed upon re-exposure to an environment, context or cue (e.g. tone, light) previously paired (Pavlovian conditioning) with an aversive unconditioned stimulus (e.g. footshock or noxious heat) and is termed conditioned SIA (a.k.a. fear-induced analgesia; fear-conditioned analgesia or conditional hypoalgesia) [7-10,32]. The tail-flick or hot plate nociceptive

tests are routinely used to assess SIA following exposure to footshock or forced swim stress paradigms [2]. Models of fear-conditioned analgesia have assessed formalin-evoked nociceptive behaviour in an aversively conditioned context [2,4,7-10,15,16,32].

3. Neurobiology of SIA

3.1. Opioids and the descending inhibitory pain pathway

Endogenous opioids play a key role in mediating endogenous analgesia. Opioid involvement in SIA was first demonstrated with the μ-opioid receptor antagonists, naloxone and naltrexone, which attenuated both unconditioned [1,37] and conditioned [4,6,37] SIA in rodents. Studies investigating morphine- and stimulation-produced analgesia provided initial evidence for the existence of endogenous descending inhibitory pain pathways [1,37]. The distribution of opioid peptides (ß-endorphin, met-enkaphalin, leu-enkaphalin and dynorphin), and their receptors (μ (mu), δ (delta), and κ (kappa)) throughout these pathways focused initial attempts to identify the receptors and neuroanatomical sites that subserve SIA [2,37].

Anatomical, pharmacological and behavioural evidence from SIA studies revealed that the amygdala, periaqueductal grey (PAG) and rostral ventromedial medulla (RVM) are critical structures in descending inhibitory pain pathways [15,16,37]. Lesions of the RVM, PAG and amygdala attenuate the conditioned SIA response [16,17]. There is, therefore, strong evidence that conditioned SIA is under supraspinal control [4], and mediated by μ and δ but not κ opioid receptors [8]. Projections from the central nucleus of the amygdala to the opioid-sensitive neurons in the PAG and RVM are suggested to be critical for expression of conditioned SIA [15]. Work in transgenic mice has demonstrated that genetic deletion/disruption of either β-endorphin [33] or dynorphin [27] abolishes the expression of forced swim SIA. Moreover, this form of unconditioned SIA could also be

attenuated by pharmacological blockade of κ opioid receptors [25] suggesting a role for κ-opioid receptors in unconditioned but not conditioned SIA. Despite this evidence in support of a role for the endogenous opioid system, early work indicated that both opioid and non-opioid mechanisms mediate SIA [37] and good progress has been made in identifying some of these non-opioid mediated mechanisms.

3.2. GABA (Gamma-amino butyric acid)

Systemic and intra-cerebral administration of anxiolytic benzodiazepines can attenuate both conditioned SIA and other conditioned fear-related behaviours [7,13]. Attenuation of these conditioned responses following local administration of benzodiazepines into the PAG and amygdala supports the view that these brain structures are part of a common fear or defensive system that is critical for antinociception and expression of fear behaviours in response to aversion [7]. Benzodiazepines bind to the $GABA_A$ receptor, and act to promote the inhibitory effects of GABA. Thus, the benzodiazepine-induced decrease in these conditioned responses indicates that the neural mechanisms underlying these processes are inhibited by GABA transmission. So, while endogenous opioids likely activate the descending analgesic pathway by inhibiting GABA release within or near the PAG and RVM, benzodiazepines reduce antinociception by potentiating GABAergic inhibition of descending inhibitory pain pathway activity [13]. Studies employing various GABA receptor agonists ($GABA_A$: muscimol; $GABA_B$: baclofen) and antagonists ($GABA_A$: bicuculline, picrotoxin; $GABA_B$: Phaclofen, CGP 35348), have established a role for both the $GABA_A$ and $GABA_B$ receptor subtypes in some forms of unconditioned SIA [35]. However, evidence on the precise roles of receptor subtypes is equivocal and dependent on the stressor employed [19] and thus further investigation into GABAergic mediation of unconditioned SIA is warranted.

3.3. Endocannabinoids

Recently, it has become apparent that another system which plays a key role in SIA is the endogenous cannabinoid (endocannabinoid) system. Experiments employing footshock paired with the tail-flick test demonstrated that the endocannabinoid system in the basolateral amygdala, PAG and RVM may mediate a non-opioid form of unconditioned SIA [18]. We and others have also demonstrated an important role for the endocannabinoid system in conditioned SIA and extinction of conditioned fear [9,26,32]. Thus, expression and extinction of conditioned fear in mice was associated with increased endocannabinoid levels in the basolateral amygdala [26] and pharmacological blockade of CB_1 receptors in the right basolateral amygdala attenuated short-term extinction of conditioned fear in rats [32]. Systemic [9] but not intra-basolateral amygdala [32] injection of the CB_1 receptor antagonist rimonabant attenuated conditioned SIA in rats. It has also been demonstrated that mice lacking the CB_1 receptor do not exhibit SIA following forced swim stress in water at 34^0C [36].

3.4. Other Substrates

Corticosterone and corticotrophin-releasing factor have been shown to mediate forced swim SIA, effects which may be related to their local anti-inflammatory actions and/or by promoting the release of opioid peptides, such as β-endorphin [23,24]. In neurotensin knockout mice, forced swim stress-induced analgesia is disrupted [5] and there is also evidence for a role of the central renin angiotensin system in analgesia following immobilization stress [14]. Finally, and not surprisingly given their important role in the descending inhibitory control of pain, a role for the monoamines has also been demonstrated in models of SIA [10,34].

4. Clinical Correlates

The first evidence for the clinical validity of the phenomenon of SIA (Table 1) came from studies by Willer and colleagues [38]. The threshold of a nociceptive flexion reflex increased with repetition of inescapable shock stress, an effect reversed by naloxone [38]. Further evidence came from a model of conditioned SIA which involved pairing auditory stimuli with a combination of mental arithmetic and white noise [11]. Both pain tolerance and threshold were elevated following re-exposure to the conditioned auditory stimulus. The conditioned effect on pain tolerance but not pain threshold was attenuated by intravenous naloxone. This lead to the conclusion that conditioned SIA in humans, as for other mammals, was both opioid and non-opioid mediated, in that when pain levels were high, the opioid system was required for analgesia but was not involved when pain levels were low [11]. Willer and colleagues also carried out additional clinical pharmacological studies which demonstrated that opioid-mediated conditioned SIA in humans was reduced by the benzodiazepine diazepam [39] and also by the quinoline derivative, PK 8165 [40]. Further parallels between the mechanisms underpinning the expression of SIA in rodents and humans comes from recent evidence suggesting a role for the hypothalamo-pituitary-adrenal axis in mediating this important survival response in humans [12].

4.1. Fear versus anxiety and the influence of attention and controllability

Although stressful stimuli decrease pain perception in humans, clinicians routinely witness that high levels of anxiety can enhance pain perception. It has been proposed that fear and anxiety represent two different psychological states which have divergent effects on pain threshold [29]. Anxiety is a future-orientated emotional state that results from a condition in which there is uncertain expectation characterised by negative affect and apprehensive anticipation of potential threats, while fear results from a situation in which there is certain expectation and is characterised by the impulse to escape.

Fear induced by acute uncontrollable shock reduced pain (measured as finger-withdrawal from radiant heat) in both unconditioned [30,31] and conditioned [30,31] SIA paradigms. Manipulating the heat stimulus at the finger, such that high intensity rapid onset constituted a predominantly spinal reflex similar to tail-flick test, whereas low intensity slower onset was used to test evaluative supraspinal nociception, provided evidence that fear can not only inhibit spinal nociceptive reflexes but also supraspinal nociceptive processes in humans [29-31]. Studies by Jansen and Arntz [20,21] focused on the interaction between anxiety and attention on SIA. In experiments employing painful electrical stimulation applied to the ankle of arachnophobes exposed to a spider cue, anxiety (high vs low) and attention (towards pain vs distracted from pain) were manipulated within subjects who received oral placebo or the μ-opioid receptor antagonist naltrexone. In the first study [20], high anxiety was associated with reduced pain ratings but this effect was lost when differences in subjective attention were corrected for. Differential effects of low and high doses of naltrexone complicated interpretation of the extent to which the analgesia observed was opioid-mediated but the authors concluded that attention, not phobic anxiety, was the predominant factor influencing pain responses in this paradigm. This conclusion was supported by a follow-up study where phobic anxiety was not associated with analgesia or alterations in plasma β-endorphin [21]. However, another important factor in these studies is the matter of controllability of the stressor.

The controllable or escapable nature of the stressor impacts both the duration of analgesia and the extent to which the opioid system is involved. Where the stressor employed is controllable, a non-opioid-mediated SIA is expressed, whereas when the stressor is uncontrollable, the resulting SIA is opioid-mediated [25]. Therefore, although phobic stressors may make subjects anxious, the experimental situation may be perceived as relatively controllable and is not associated with opioid mediated-analgesia [21]. In contrast, when subjects were exposed to a more uncontrollable stress

situation, that of a first time parachute jump for example, an opioid-mediated analgesia was observed [22]. Similarly, study of SIA in war veterans with post traumatic stress disorder (PTSD), demonstrated that re-exposure to a stimulus resembling the original traumatic event increased pain tolerance to a heat stimulus, an effect which could be attenuated by prior administration of naloxone [28]. It appears, therefore, that activation of the endogenous opioid system during SIA is dependent not only on exposure to aversive stimuli, but also requires that the stimulus be uncontrollable or a perception that this is the case.

5. Conclusion

In summary, there has been significant progress in our understanding of SIA in recent years but difficulties still arise in understanding subjective individual pain experiences. The contribution of attentional and affective factors attributed to the modality of the stressor, its context or the pain test employed, further complicates matters. The majority of clinical studies have focused on pharmacological manipulation of the endogenous opioid system and results obtained correlate strongly with data amassed from animal studies. However, there is a relative paucity of clinical studies investigating the role of other substrates shown to mediate SIA in laboratory animals including the GABAergic, cannabinergic and monoaminergic systems, and further clinical studies on these systems is warranted. Furthermore, human functional imaging methodologies, which have significantly enhanced our understanding of attentional or anticipatory modulation of pain, have yet to be applied to the study of SIA. Increased understanding of the neuroanatomy, neurochemistry and neuropharmacology of SIA will illuminate our understanding of endogenous analgesic and aversive systems. The long-term challenge is to harness our knowledge of the mechanisms underlying this form of profound, potent analgesia to develop improved pharmacological and psychological approaches to treat pain.

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6. References

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