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Abbreviations: SIA, stress-induced analgesia; FCA, fear-conditioned analgesia; GABA, γ-aminobutyric acid; HA, high analgesia; LA, low analgesia; fMRI, functional magnetic resonance imaging; DNIC, diffuse noxious inhibitory control; PAG, periaqueductal grey; RVM, rostroventral medulla; 5-HT, 5-hydroxytryptamine; CB_1, cannabinoid type 1; CB_2, cannabinoid type 2; NMDA, N-methyl-D-aspartic acid; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; mGluR, metabotropic glutamate receptor; NK1, neurokinin 1; SP, substance P; 2-AG, 2-arachidonoylglycerol; FAAH, fatty acid amide hydrolase; MGL, monoacylglycerol lipase; HPA, hypothalamo-pituitary-adrenal; ACTH, adrenocorticotropic hormone

Stress-Induced Analgesia

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ABSTRACT

For over 30 years, scientists have been investigating the phenomenon of pain suppression upon exposure to unconditioned or conditioned stressful stimuli, commonly known as stress-induced analgesia. These studies have revealed that individual sensitivity to stress-induced analgesia can vary greatly and that this sensitivity is coupled to many different phenotypes including the degree of opioid sensitivity and startle response. Furthermore, stress-induced analgesia sensitivity can vary a great deal depending on age, gender, and prior experience to stressful, painful, or other environmental stimuli. Stress-induced analgesia is mediated by activation of the descending inhibitory pain pathway. Pharmacological and neurochemical studies have demonstrated involvement of a large number of neurotransmitters and neuropeptides. In particular, there are key roles for the endogenous opioid, monoamine, cannabinoid, γ-aminobutyric acid and glutamate systems. The study of stress-induced analgesia has enhanced our understanding of the fundamental physiology of pain and stress and has been a useful approach for uncovering new therapeutic targets for the treatment of pain and stress-related disorders.

1. Introduction

Stress-induced analgesia (SIA) is an in-built mammalian pain suppression response that occurs during or following exposure to a stressful or fearful stimulus. Experimental models of this response help to elucidate the fundamental mechanisms of nociception and aversion as well as potential therapeutic targets for pain and stress-related disorders. The present manuscript is an update of earlier reviews on this topic published in the 1980's (Akil *et al.*, 1986; Amit and Galina, 1986; Bodnar, 1986; Hayes and Katayama, 1986; Terman and Liebeskind, 1986; Terman *et al.*, 1984). We include discussion of the most important findings pre-1986 together with extensive review of the body of work published on this topic since mid-1980. The manuscript will cover literature on the anatomical, neurochemical and molecular mechanisms underlying reduced nociceptive signaling following exposure to aversive stimuli. We will also highlight areas where further research is needed. We begin with an introduction to the evolutionary implications of the relationship between pain, stress and anxiety along with the genetics of SIA. Animal and human models employed to study stress- or fear-induced analgesia will then be reviewed followed by a description of the neuroanatomical substrates which have been shown to play a role in mediating and modulating endogenous analgesia through the descending inhibitory pain pathway. We then present the evidence for involvement of the opioid, GABAergic, glutamatergic, monoaminergic, cannabinergic systems in stress- or fear-induced analgesia. The review concludes with a discussion of the importance of this phenomenon in the pre-clinical study of the fundamental mechanisms of pain and fear/anxiety/stress and its potential clinical significance.

2. The evolutionary perspective and genetics of stress-induced analgesia

Pain can be considered as an evolutionarily developed defence response to an aversive or noxious stimulus. Aversive behaviours (e.g. fear, anxiety, panic), or behaviours to avoid pain, may be viewed as part of an organism's defence system against stimuli that could cause pain (Bolles and Fanselow, 1980). Thus, nociception and aversion have overlapping characteristics. The overlap is readily apparent at the neural pathway and substrate level.

Historically, pain and aversion have been studied as two separate entities. However, studies in rodents addressing the link between the two showed a reduction in nociceptive behaviours upon exposure to aversive stimuli (Akil *et al.*, 1976a; Madden *et al.*, 1977) including stimuli associated with learned fear (Calcagnetti *et al.*, 1987; Chance *et al.*, 1978; Finn *et al.*, 2004; Finn *et al.*, 2006; Harris and Westbrook, 1995; Helmstetter and Fanselow, 1987a, b; Roche *et al.*, 2007). SIA is also expressed in humans (Flor *et al.*, 2002; Flor and Grusser, 1999; Willer *et al.*, 1981) and studies of the mechanisms involved in rodent models of SIA are likely to be relevant in humans.

From an evolutionary perspective, SIA may be thought of as a component of the fight or flight response. Tending to a painful injury would not be conducive to the survival of an organism if further injury or death were threatened. Once the organism is no longer in

danger however, elevated nociception, expressed upon extinction of the aversive response, could be beneficial as normal behaviours may aggravate the injury.

Predator-prey interactions most likely played a major role in the evolutionary development of SIA. Predators tend to prefer injured prey. Predator preference for injured prey, based on maximizing energy expenditure to consumption efficiency, may have lead to a selective pressure for the evolution of animals which express SIA in threatening situations.

Mice selectively bred for either a high sensitivity (HA) or a low sensitivity (LA) to SIA initiated by swim tests followed by the tail-flick test of nociception have been the primary models utilized to find a genetic basis for this phenomenon (for review see Panocka *et al.*, 1986b). Studies dating back to the mid-1980's by Sadowski and collaborators on these two groups of mice found several phenotypical differences resulting from differences on relatively few genetic loci (Blaszczyk *et al.*, 2000; Kest *et al.*, 1999; Konarzewski *et al.*, 1997; Lapo *et al.*, 2003b; Lutfy *et al.*, 1996; Marek *et al.*, 1993; Mogil *et al.*, 1995b; Mogil *et al.*, 1996a; Panocka *et al.*, 1986a, 1991; Sacharczuk *et al.*, 2003; Sacharczuk *et al.*, 2008; Sadowski and Konarzewski, 1999; Sadowski and Panocka, 1993). HA mice displayed an increased sensitivity to morphine and opioid receptor antagonists suggesting a greater degree of involvement of the endogenous opioid system than LA mice (Kest *et al.*, 1999; Marek *et al.*, 1993; Panocka *et al.*, 1986a, 1991; Sadowski and Panocka, 1993). HA mice also displayed a higher startle response to a loud acoustic tone, greater susceptibility to mutagenesis following whole-body gamma-

radiation, greater susceptibility to hypothermia and a lower oxygen consumption during a cold swim, lower core body temperature, lower activity in an open-field test, and a lower propensity to consume alcohol following chronic mild stress compared to LA mice (Blaszczyk *et al.*, 2000; Konarzewski *et al.*, 1997; Lapo *et al.*, 2003a, b, c; Mogil *et al.*, 1996a; Sacharczuk *et al.*, 2003; Sacharczuk *et al.*, 2008; Sadowski and Konarzewski, 1999). Efforts to find a genotypic basis for these differences have yielded some surprising results. First, cross-breeding of HA mice with mice highly sensitive to morphine yielded some reversal of HA and some "super-HA" mice; meanwhile, cross-breeding LA mice with mice with low sensitivity to morphine yielded some reversal of LA and some "super-LA" mice which suggests that morphine sensitivity and SIA sensitivity are produced by different genetic loci (Mogil *et al.*, 1995a). Second, a study showed that LA mice typically have higher brain regional levels of μ- and δ-opioid receptor mRNA than HA mice (Kest *et al.*, 1999) in contrast to an earlier study which reported an increase in μ-opioid receptor binding in the medial thalamus of HA mice compared with LA mice (Mogil *et al.*, 1994). Third, despite the numerous phenotypic differences between HA and LA mice, only one or two genetic loci appear to mediate sensitivity to SIA according to a study using Mendelian genetics and the appearance of these divergent SIA-related phenoytpes can occur after only one generation (Mogil *et al.*, 1995b). However, complete abolition of SIA required more than 21 generations of selective breeding (Mogil *et al.*, 1996b). Thus, the genetic basis for stress-induced analgesic sensitivity is not well conserved but the fundamental genetic basis for the existence of SIA is very well conserved.

3. Models of Stress-induced Analgesia (SIA)

Research into the mechanisms of SIA elucidates the complex physiological mechanisms of pain, stress, and fear while at the same time identifying potential new therapeutic targets for disorders associated with these phenomena. The next section will review models of SIA including unconditioned SIA and conditioned SIA (also known as conditional analgesia or fear-conditioned analgesia; FCA) as well as some models of distraction-induced analgesia where appropriate.

3.1. Unconditioned SIA

Two stimuli are needed to model SIA – a noxious stimulus and an aversive stimulus (Table 1). The aversive stimulus can be an unconditioned or a conditioned stimulus. During unconditioned SIA, an unconditioned stressful stimulus or environment is used to induce analgesia before or during exposure to a noxious stimulus. Unconditioned aversive stimuli that have been used in these models include footshock, forced swimming, cold water immersion, infantile isolation, exposure to a novel arena, elevated plus maze, social conflict, or predators such as biting mice, biting flies, cats, or snakes. In humans, unpleasant visual stimuli, hypnosis and acupuncture have been utilized. In rodents, invasive procedures have also been used to elicit an unconditioned aversive response. These include direct electrical or pharmacological stimulation of several

different brain regions and seizure induction. Noxious stimuli utilized also vary depending on the model and species. These include injection of the chemical irritant formalin, radiant heat, insect bites, tail pinches, and intracutaneous electrical current (Table 1).

3.2. Conditioned SIA (also known as conditional analgesia or fear-conditioned analgesia; FCA)

Fear-conditioned analgesia (FCA) may be defined as a survival response that is expressed as a suppression of pain upon re-exposure to a context or cue previously paired with a noxious or aversive stimulus. Thus, FCA arises through Pavlovian conditioning. FCA is characterised by a robust decrease in nociception in rodent models which, at its peak, can suppress behaviours associated with pain by greater than 90% (Finn *et al.*, 2004; Harris and Westbrook, 1995). Conditioned aversive stimuli that have been used in models of FCA include re-exposure to an arena/context previously paired with footshocks or noxious thermal stimulation, or a light paired with mental arithmetic and white noise. A study has also shown that mice are capable of social learning of conditioned fear to biting insects, with such conditioning capable of eliciting an analgesic response (Table 1).

3.3. The importance of the type of noxious and aversive stimuli

Pain research has shown that (1) not all noxious stimuli are processed centrally or peripherally in the same way and (2) not all aversive stimuli are capable of eliciting an

analgesic response and can in fact elicit a hyperalgesic response. Contrasting events occur in mammals experiencing acute pain versus chronic pain (Craig, 2006). Studies have shown that rats which are in chronic pain rather than acute pain express elevated pain behaviours in the presence of an aversive stimulus (Rivat *et al.*, 2007). Children who experience the chronic stress of recurrent abdominal pain display lower levels of SIA (Dufton *et al.*, 2007). In this latter study, children were exposed to a stress interview or a stressful serial subtraction test but displayed lower levels of pain tolerance to the cold pressor test. However, the effects of chronic, unpredictable stress on SIA appear to be species and/or stress specific. For example, an analgesic effect in the tail-flick test of nociception was observed in both young and old male rats which were exposed to chronic stress of forced swimming or overcrowding over a period of 21 days (Pinto-Ribeiro *et al.*, 2004).

Caution should be exercised when interpreting the results of studies that utilise tests of thermal nociceptive responding to model SIA. Studies have shown that stress can cause vasoconstriction in the tail and paws which can lead to a reduction in skin temperature (Blessing, 2003; Garcia *et al*., 2001; Vianna and Carrive, 2005). Stress-induced increases in tail-flick or paw withdrawal latency may then be related, at least in part, to the stress-induced reduction in skin temperature at the time the noxious thermal stimulus is applied. The contribution of change in skin temperature to drug-induced alterations in behavioural responding to noxious thermal stimuli has been demonstrated (Eide and Tjølsen, 1988). A psychophysical study employing infrared thermography to monitor local changes in tail temperature suggests that most of the delay between the application of the thermal

stimulus and the behavioral reaction can be attributed to the physical process of heating the skin (Benoist *et al*., 2008). Tjølsen and colleagues, however, also proposed an improved method for tail-flick testing which addresses this potential confound by measuring tail temperature close to the heated area (Tjølsen *et al*., 1989). Thus the extent to which fluctuations in skin temperature may complicate response latency can be limited with the test apparatus used, as some suppliers, for example, now offer a means to (a) monitor tail temperature during the tail-flick test and (b) use a trigger temperature function whereby the tail is warmed to a pre-set temperature prior to commencing the test. Moreover, that a stress-induced increase in withdrawal latency to a thermal stimulus may, in part, be due to stress-induced changes in skin temperature arising from vasoconstriction does not in itself preclude an interpretation of stress-induced analgesia, if one considers analgesia in the context of the body's general homeostatic mechanisms, and provided care is taken when considering the anatomical or physiological origins of the analgesia.

As already stated, SIA does not occur in response to all aversive stimuli and various aversive stimuli have been shown to increase nociception. It has been suggested that the anticipation of pain activates brain regions in close proximity to brain regions activated by pain itself (Ploghaus *et al.*, 1999). In an interesting human study, subjects were given visual cues to an impending noxious stimulus (Ploghaus *et al.*, 2001). One group of subjects was given a consistent moderate noxious stimulus following a visual cue while another group was given random and intermittent noxious stimuli mixed with the

moderate stimulus following a visual cue. This erratic stimulus intensity increased the aversiveness of the environment, but also increased the perception of the moderate noxious stimuli as being painful – the opposite of SIA. In a study of a similar nature, a significant reduction in pain score was observed when the subjects were allowed to control the onset of a noxious stimulus compared to subjects under external control of the noxious stimulus (Wiech *et al.*, 2006). The lack of control created an additional aversive component, so the increase in pain under this condition seems counter-intuitive to what is known about SIA. One possible explanation for these differing responses, as demonstrated in multiple human studies (Meagher *et al.*, 2001; Rhudy and Meagher, 2000, 2001), is that the induction of anxiety can increase sensitivity to pain while the induction of fear decreases sensitivity to pain.

It has been shown that illness induced by lithium or lipopolysaccharides results in hyperalgesia in the rat formalin and tail-flick tests (Wiertelak *et al.*, 1994). Furthermore, and quite remarkably, systemic, spinal or supraspinal administration of the opioid receptor antagonist naloxone blocks illness-induced hyperalgesia (McNally *et al.*, 2000). This is remarkable because studies from over 30 years ago to present have shown that naloxone also blocks the hypoalgesic effect of SIA (Akil *et al.*, 1976b; Madden *et al.*, 1977). The authors state that the attenuation of hyperalgesia with naloxone suggests a role for opioid receptors in the descending facilitation of pain.

Activation of endogenous analgesic mechanisms can be achieved where the aversive stimulus does not induce fear and is questionably stressful as Amit and Galina (1986)

pointed out in their review. Such stimuli can be considered distracting rather than aversive. However, because of the similarities between SIA and distraction-induced analgesia at the neural and molecular levels, studies of this nature will also be discussed in this review. Traditional distracting stimuli which have been utilised include listening to music (Fowler-Kerry and Lander, 1987), counting objects (Zeltzer *et al.*, 1991) and light centrifugal rotation (7.0 transverse *g*'s) (Hayes *et al.*, 1978). Rat and human studies have shown dramatic increases in pain threshold upon vaginal stimulation (Komisaruk and Wallman, 1977; Whipple and Komisaruk, 1985). In addition, human studies with patients who were experiencing procedural dental/periodontal pain showed a marked reduction in their subjective pain ratings when placed in a virtual reality environment (Hoffman *et al.*, 2001). There is also a study which shows that children which have suffered acute burn injuries have reduced pain levels when pharmacological management of pain is coupled with virtual reality game playing (Das *et al.*, 2005). A recent study from our laboratory using a rat model utilised a novel arena or novel object as stimuli to distract attention away from formalin-induced pain (Ford *et al.*, 2008). These studies demonstrate that non-aversive stimuli are capable of eliciting analgesia, possibly by distracting attention away from the source of pain (Eccleston and Crombez, 1999).

3.4. Gender-related differences in the expression of SIA

Studies have shown that gender-related differences in the expression of SIA exist (for review see Sternberg and Liebeskind, 1995). Similar to analgesia initiated by most other types of stimuli (Bodnar *et al.*, 2002), males tend to exhibit higher SIA than females. For

example, in a study which used two rat models of SIA, one induced by a continuous cold-water swim and the other by intermittent cold-water swim, female rats expressed a significantly lower analgesia (Romero and Bodnar, 1986). Gonadectomised or castrated males expressed similar levels of analgesia as intact females suggesting a role for gonadal steroids in mediating the gender-related differences in expression of SIA (Romero *et al.*, 1987). These workers also provide evidence that suggests the role of the opioid system in mediating SIA is gender-specific (Romero *et al.*, 1988). The sensitivity to SIA in female rats appears to be dependent upon the estrous cycle and on the model of SIA. For example, during estrous, females exhibited a significant reduction of opioid SIA but only a small reduction in non-opioid SIA compared to other times in their cycle (Ryan and Maier, 1988). This study also shows that SIA in females is modulated by ovarian hormones as ovariectomised subjects exhibited reduced opioid-dependent SIA, an effect reversed with estrogen administration. It is therefore apparent that variation in sensitivity to SIA in both males and females can occur with fluctuations in gender-specific hormones.

3.5. The effects of age and experience on SIA

There have been many studies which have shown that age and experience influence the expression of SIA. Regarding age, however, there is no clear pattern of increased or decreased sensitivity to SIA as the subject grows older. One study has shown that the development of analgesia induced by water immersion occurs in rats as young as 3 days old with a significant increase in analgesia by 17 days (Stolberg and Frenk, 1995). These

workers propose that the increase in analgesia at this age is due to the development of supraspinal descending pain inhibition. Tolerance to SIA, as measured by the tail-flick test, was acquired and maintained faster in younger (4 months) rats than older (15-16 months) rats following repeated cold-water swim tests over 15 days (Girardot and Holloway, 1985). These authors also report that tolerance to SIA occurred faster in younger rats when the tests were spaced 5-months apart. Furthermore, 9-month old rats, which had been exposed repeatedly to the cold-water swim test when 4-months old, expressed an increased tolerance to SIA than counterparts which were not exposed previously to the cold-water swim test. Another study with rats also observed an age-related increase in SIA, an effect attenuated with long-term exposure to Acetyl-L-Carnitine which the authors suggest prevented an age-related loss in hippocampal glucocorticoid receptors (Ghirardi *et al.*, 1994). In contrast, mice which received a painful injection of formalin into the hindpaw displayed significantly higher SIA at an early age (4 > 24 > 48 weeks) when coupled with forced walking stress (Onodera *et al.*, 2001). The age-related differences in this study were shown to be non-opioid mediated but were NMDA receptor dependent. Other studies suggest, however, that non-opioid mediated SIA which is potentiated following adrenalectomy, is not age-specific (Hamm and Knisely, 1987; Hamm *et al.*, 1986). A study with human volunteers shows an age-related decline in SIA (Washington *et al.*, 2000). In this study, electrical and thermal nociceptive stressors elicited an analgesic response in the cold pressor test. In summary, it would appear that the influence of age on SIA depends on the species and/or the type of painful or stressful stimuli which can mediate SIA through different signalling systems.

We refer to experience in the following section as an exposure to any number of stressful, painful, or pharmacological/chemical stimuli which occurred either prenatally or postnatally during the life of the organism. The exposure in these cases would occur prior to the testing of SIA sensitivity. Rats which were exposed to morphine as neonates (1-7 days old) expressed a transient increase in analgesia with intermittent cold-water swim and a transient decrease in analgesia following a continuous cold-water swim at a later stage in life (Arjune and Bodnar, 1989). Rats which were undernourished from day 14 of gestation until 50 days of age exhibited significantly reduced SIA from both restraint and forced swim stress (Gutierrez and Keller, 1997). REM sleep deprivation has also been shown to reduce analgesia induced by a cold-water swim in rats (Ukponmwan *et al.*, 1984). Exposure of rats to ethanol in the prenatal stage significantly enhanced opioid-mediated SIA when offspring were 150-210 days of age (Nelson *et al.*, 1985). However, another study has shown that postnatal ethanol exposure has no effect on opioid-mediated SIA and decreases non-opioid-mediated SIA in mice (Bell *et al.*, 1998). Female rats, whose mothers had been exposed to heat and restraint stress during their gestation, exhibited reduced SIA assessed with the tail-flick test following continuous cold-water swim stress (Kinsley *et al.*, 1988). Similarly, male rats, whose mothers had been exposed to footshocks every other day during their gestation, showed a reduction in SIA at the age of 14 days (Takahashi *et al.*, 1990). Furthermore, male rats which experienced maternal separation for 180 minutes a day as neonates exhibited increased pain responses to the tail flick test following acute 60 minute water avoidance stress at 2 months of age (Coutinho *et al.*, 2002). Another study with mice confirmed a decrease in SIA for both sexes when exposed to prenatal stress (Sternberg, 1999). An interesting

clinical study showed that female smokers had reduced pain sensitivity compared to female non-smokers, but female smokers did not express SIA whereas female non-smokers did express SIA (Girdler *et al.*, 2005). Thus, it appears evident that the influence of experience can either increase or decrease the sensitivity of the subject to SIA depending on the type of experience, when the experience occurred, the type of species, and the type of model used for SIA.

3.6. Diffuse noxious inhibitory control

Diffuse noxious inhibitory control (DNIC) describes the strong inhibition of neurons in the dorsal horn of the spinal cord when a nociceptive stimulus is applied to any part of the body, distinct from their excitatory receptive fields (Dickenson *et al*., 1981; for review see Villanueva and Le Bars, 1995). DNIC manifests as a decrease in pain sensation to a noxious stimulus applied to one part of the body during or following application of another noxious stimulus to a different part of the body. It follows then, that DNIC shares conceptual similarities with SIA and some models of SIA involve exposure to noxious stimuli followed by subsequent tests of responding to additional noxious stimuli (Table 1). DNIC, like SIA, has been demonstrated in rodents (Dickenson *et al.*, 1981) and humans (Chen *et al.*, 1985; Le Bars *et al.*, 1992; Talbot *et al.*, 1989). But while there may be some overlap between the mechanisms mediating DNIC and SIA where the stressor employed is a noxious stimulus, it is also clear that the two phenomena, DNIC and SIA, can be dissociated at the neuroanatomical level. Work by Le Bars and colleagues has shown that DNIC is primarily mediated at the spinal level

(Dickenson and Le Bars, 1987). Experiments aimed at elucidating the role of supraspinal components of the descending inhibitory pain pathway failed, in most cases, to demonstrate a role for brain regions known to play key roles in SIA. For example, lesions of the midbrain periaqueductal grey (PAG) (Bouhassira *et al.*, 1992b), rostral ventromedial medulla (RVM) (Bouhassira *et al.*, 1993) or locus coeruleus (Bouhassira *et al.*, 1992a) did not modify DNIC in rodents. By contrast a role for the caudal medulla-spinal connectivity has been demonstrated (Bouhassira *et al.*, 1995) and, lesions of subnucleus reticularis dorsalis in the caudal medulla strongly reduce DNIC (Bouhassira *et al*., 1992c). As with SIA, there is evidence for a role of the opioid (Bouhassira *et al.*, 1988; Le Bars *et al.*, 1987; Willer *et al.*, 1990) and serotonergic systems (Dickenson *et al.*, 1981) in DNIC. Thus, while these two forms of endogenous analgesia can be separated neuroanatomically, there may be a degree of convergence at the level of neurotransmitters/neuropeptides. While it is conceivable that both phenomena, SIA and DNIC, may contribute to the antinociception observed during or following exposure to noxious stimuli, clearly DNIC would not be a consideration in models of SIA which utilise non-noxious physical or psychological stressors.

3.7. The complexity of SIA in human studies

Simple observations of human behaviour suggest an ability to train sensory perception. The motivation and ability to train oneself to suppress pain can vary greatly between individuals. For example, individuals competing in athletic competitions could face reduced monetary rewards if it is believed they cannot endure the physical demands.

Other individuals simply take pride in their ability to endure pain. Furthermore, a study has shown that some individuals react to attempts to induce fear with humour (Rhudy and Meagher, 2003). These personality differences can influence the expression of SIA.

A similar observation has been observed in a study which utilised real-time functional magnetic resonance imaging (fMRI) to train individuals to increase their pain threshold (deCharms *et al.*, 2005). In this study, individuals learned to deliberately activate pain controlling regions of their brain, such as the rostral anterior cingulate cortex, in the complete absence of an aversive stimulus in such a manner that pain perception in response to a noxious thermal stimulus eventually becomes reduced. In another study, subjects were presented with a color visual cue followed by heat stimulation and were asked to focus and distract themselves from the noxious heat (Tracey *et al.*, 2002). The distracted group rated the thermal intensity significantly lower than the attentive group. The distracted group also showed significantly greater activation of the periaqueductal grey (PAG) as measured with fMRI. This would suggest that it is possible to alter pain sensitivity through intentional activity which in turn activates the PAG. The variation of pain perception across individuals is a possible confounding factor in studying SIA in humans. As mentioned earlier, human anticipation of a noxious stimulus can confound the noxicity of the stimulus and while the exact mechanistic question being explored may not be known to the subjects, ethical guidelines require that they are aware they are in a "pain" experiment. This differs from animal studies where subjects are almost certainly unaware of the nature of the stimulus they are about to experience. This complication, together with inter-subject differences in perception of stressful or aversive stimuli,

presents additional opportunities for variability between human subjects in studies of SIA. Thus, the psychological, as well as the genetic impact of pain and the fear of pain can vary between subjects in human studies. The detailed molecular and neural mechanisms underpinning this variation are beyond the scope of this review, but have been reviewed by others (Calder *et al.*, 2001; Mogil *et al.*, 1996b; Price, 2000).

Individual variability exists to some extent in all species which express SIA. Concerning experimental design for models of SIA, this usually means a larger number of subjects per experimental group would be required to establish significance than in other non-behavioural biological experiments. An ideal model of SIA would allow for assessment of the effects of combining the aversive stimulus with a painful stimulus and the effects of the aversive stimulus and painful stimulus separately. Furthermore, care must be taken that the aversive stimulus does not cause pain at the time of testing. The mechanisms underlying SIA and FCA are similar. Monoaminergic (Finn *et al.*, 2006), endocannabinoid (Finn *et al.*, 2004; Hohmann *et al.*, 2005; Valverde *et al.*, 2000), and opioid (Akil *et al.*, 1976b; Lewis *et al.*, 1980; Madden *et al.*, 1977) systems appear to play significant roles in all these models through the modulation of the descending inhibitory pain pathway. In addition, evidence suggests that GABAergic and glutamatergic signalling in discrete brain regions is involved in SIA. These neurochemical mechanisms will be discussed later but we first provide an overview of the key neuroanatomical substrates and pathways mediating SIA.

4. Neural substrates involved in SIA

In the 17th century, René Descartes proposed a "specificity theory" which stated that pain intensity and tissue damage are directly related. This theory was generally accepted for many years despite the fact that pain could be modulated by many factors, including experience and emotional state, and the existence of phantom-limb pain in amputees. The gate-control theory, first described by Melzack and Wall in 1962, postulated that pain is modulated by the interaction between neurons at the spinal level and not by a direct activation of pain receptors (Melzack and Wall, 1962). The gate-control theory suggests that non-nociceptive Aβ fibres form synapses at laminae along with nociceptive Aδ and C fibres (Melzack and Wall, 1965). Firing of Aβ fibres would thus "close the gate" to nociceptive signalling. Conversely, firing of nociceptive fibres would inhibit transmission of non-nociceptive signalling and would "open the gate." The theory of gate-control provided a considerable advancement in the understanding of pain modulation. However, it was not until the gate-control theory was subsequently integrated with the modulation of pain by descending pain pathways that a supraspinal modulation of pain was considered (Liebeskind and Mayer, 1971; Mayer and Price, 1976; Mayer *et al.*, 1971).

Supraspinal modulation of pain can comprise either the enhancement of nociception, known as descending facilitation (Willer *et al.*, 1979), or the reduction of nociception, known as descending inhibition (Mayer *et al.*, 1971). Interestingly, the substrates and anatomical regions involved in facilitation and inhibition of nociception are often

identical. As Millan (2002) points out in his extensive review of the descending control of pain, the difference in the mechanisms of facilitation and inhibition of nociception are primarily in receptor subtypes coupled to differing intracellular mechanisms. Spinal pathways, through mechanisms elaborated from the gate-control theory, and supraspinal descending inhibitory pain pathways, both play a role in mediating SIA (Grau, 1987; Grau *et al.*, 1990; Madden *et al.*, 1977; Meagher *et al.*, 1993; Meagher *et al.*, 1990; Rhudy *et al.*, 2004; Watkins and Mayer, 1982).

Primary afferent neurons in or around the epidermis detect painful stimuli which may be chemical, thermal, or mechanical in nature (Figure 1). The primary afferent neurons project and transmit the nociceptive information to the dorsal horn of the spinal cord. Nociceptive information is then relayed either directly to the cortex or indirectly to the cortex through the brainstem, midbrain, and thalamus via the ascending pain pathways (for review see Millan, 1999). Descending pain pathways originate in the cortex or hypothalamus and terminate in the spinal cord (for review see Millan, 2002). Neurons in the cortex also relay nociceptive information to the amygdala, hypothalamus or directly to the PAG.

The following sections will review the evidence supporting an involvement of specific neural regions in SIA. The studies to be described utilized imaging, stimulation, lesions, or administration of non-specific synapse blockers to elucidate role of specific regions. In the stimulation studies, the stimulation, when correlated with a hypo- or hyperalgesic effect, takes the place of an external aversive stimulus. Also included in the following

sections are studies which show region-specific alterations in immediate early response genes during SIA.

4.1 Brain regions

4.1.1. Cortex

The neurons of the primary somatosensory cortex function to discriminate between nociceptive signals (Libet, 1982) whereas neurons in the medial prefrontal cortex are able to encode stimulus intensity (Zhang *et al.*, 2004). The prefrontal cortex has also been implicated in the recall and extinction of fear-related memory of noxious stimuli (Hugues *et al.*, 2004). Studies examining the effects of electrical stimulation of cortical regions suggested a role in pain processing. Electrical stimulation of the cingulum bundle and surrounding cortical tissue before and after a formalin injection in rats produced significant reductions in pain behaviours during both phases of the formalin test (Fuchs *et al.*, 1996). Another study reported similar effects using the hot plate and tail reflex test in male rats after stimulation of the medial prefrontal cortex, but no increase in pain threshold after stimulation of the occipital and cerebellar cortices (Hardy, 1985). Orbital cortex stimulation in rhesus monkeys resulted in moderate elevations in pain threshold elicited by a noxious tooth shock (Oleson *et al.*, 1980). Taken together, these studies suggest that activation of the cortical brain regions by direct stimulation can mediate pain reduction similar to that seen in SIA.

Meagher *et al.* (1989) showed that lesions to the frontal cortex abolished SIA induced by brief, but not long, footshocks in rats. Further studies report that bilateral lesions of the ventrolateral orbital cortex attenuated the inhibition of pain caused by high intensity electroacupuncture during the tail flick reflex test in rats (Lu *et al.*, 1996). However, analgesia induced by low intensity electroacupuncture was not affected by the lesions in this study. Electroacupuncture of low and high intensity increased the pain threshold to radiant thermal heat in a human study (Zhang *et al.*, 2003a). fMRI revealed a positive correlation between the analgesic effect and activity in the ipsilateral anterior cingulated cortex. In a similar study that used a cold thermal noxious stimulus, electroacupuncture significantly increased activation of the bilateral secondary somatosensory area, medial prefrontal cortex and the Brodmann area 32 while decreasing activation of the primary somatosensory Brodmann area 7 and 24 (Zhang *et al.*, 2003b). Furthermore, in a human study using a visual incongruent colour-word Stroop task as a distraction, significant reductions in pain intensity and unpleasantness to a noxious heat stimulus were observed (Valet *et al.*, 2004). These effects correlated with an increased activation of orbitofrontal and perigenual anterior cingulate cortex compared to non-distracted subjects. In addition, this study showed that the orbitofrontal cortex facilitated an analgesic state through an interaction with the PAG as the pain state without distraction did not show high activity in these regions.

4.1.2. Hippocampus

There is a paucity of studies examining the role of the hippocampus in SIA despite its well established role in both pain and stress (for reviews see Maren, 2001; McEwen, 2001). A recent study has shown a role for the cholinergic, opioidergic, and GABAergic systems in mediating nociceptive transmission in the dorsal hippocampus of guinea pigs (Favaroni Mendes and Menescal-de-Oliveira, 2008). Lesions of the ventral hippocampus in neonate rat pups impaired long-term development of nociceptive signalling as an increased latency was observed during the hot plate, paw pressure and tail flick tests (Al Amin *et al.*, 2004). Lesion studies have also confirmed the role of the hippocampus in the fear response and that it depends on (a) the subregion lesioned (b) when it is lesioned and (c) what type of fear-behaviour is being investigated (i.e. acquisition, expression, consolidation, re-consolidation, extinction) (for review see Fanselow, 2000; Hobin *et al.*, 2006; Kim *et al.*, 1995; Kim and Fanselow, 1992; Lehmann *et al.*, 2007; for review see Maren and Holt, 2000; Matus-Amat *et al.*, 2004; Sutherland *et al.*, 2008).

The septo-hippocampal system is highly involved in nociceptive neurotransmission (for review see Aloisi, 1997) and lesions to the ventromedial septum reduce SIA and FCA in rats (Kelsey and Baker, 1983). In a human study by Zhang *et al*. (2003a), electroacupuncture of low and high intensity increased the pain threshold to radiant thermal heat. A negative correlation between the analgesic effect and neuronal activity in the bilateral hippocampus as measured by fMRI was observed. However, to date no

studies have directly investigated the role of the hippocampus in SIA despite the evidence for a role of the hippocampus in pain and stress.

4.1.3. Amygdala

The amygdala has been shown to play a pivotal role in mediating conditioned and unconditioned fear, pain signalling, and SIA. An early study in guinea pigs showed that electrical stimulation of the amygdala may be algesic or analgesic, depending on the subregion stimulated (Lico *et al.*, 1974). More recently, studies showed that electrical stimulation of the amygdala resulted in a reduction in nociception induced by formalin in rats (Mena *et al.*, 1995) and a reduction in nociception during tooth pulp stimulation in cats (Kawarada *et al.*, 1996). Electrical stimulation of the amygdala has also been demonstrated to enhance the startle reflex to an acoustic tone in rats (Rosen and Davis, 1990).

A key role for the amygdala in SIA has been demonstrated. Lesions to the central amygdala attenuated unconditioned SIA in rats following twenty minutes of regular, intermittent footshocks (Werka, 1994, 1997; Werka and Marek, 1990). A study by Helmstetter (1992) showed that lesion of the amygdala also attenuated FCA. Moreover, Watkins *et al*. (1993) showed that lesions to the central amygdala of rats could attenuate FCA. However, in the same study these authors reported that unconditioned SIA in rats is not affected by lesions to the amygdala. This finding contrasted with another study which showed that bilateral lesions to the amygdala attenuated SIA in rats following

multiple environmental challenges, such as cat exposure and acute footshock, while confirming the role of the amygdala in FCA (Fox and Sorenson, 1994). Further studies also confirmed that the amygdala is needed for SIA as basal jump thresholds following a cold-water swim were significantly increased following lesions of the amygdaloid complex in rats (Pavlovic *et al.*, 1996). Taken together, these studies suggest that the amygdala mediates SIA elicited with almost any type of stressor.

In the human study by Zhang *et al*. (2003a) discussed in the previous section, a negative correlation between the analgesic effect and neuronal activity in the contralateral amygdala as measured by fMRI was observed during tests with electroacupuncture of low and high intensity to increase the pain threshold to radiant thermal heat (Zhang *et al.*, 2003a). . Electroacupuncture also increased the tail-flick latency in rats and this corresponded to an increase in c-Fos expression in the central amygdala (Dai *et al.*, 1992).

The amygdala receives nociceptive input from the primary somatosensory cortex and can either transmit or receive nociceptive information from the midbrain PAG (Helmstetter *et al.*, 1993).

4.1.4. Periaqueductal grey

Neuronal projections from the PAG modulate aversive and nociceptive signalling and mediate SIA. A study by Mayer and Liebeskind (1974) showed that direct stimulation of the PAG eliminated responsiveness to various noxious stimuli such as electric shock, tissue destructive pinch, and radiant heat applied to the tail. In a later study, a significant reduction in the pain response to formalin injection with PAG stimulation was also observed (Dennis *et al.*, 1980). This suggested that the PAG was an essential component of the descending inhibitory pain pathway.

Helmstetter and Tershner (1994) also reported an elimination of antinociceptive signalling with lesions to either the dorsal or ventral PAG in their rat FCA model. Infant rats with lesions of the lateral or ventrolateral PAG displayed less SIA when their forepaw was exposed to heat coupled with the stress of social isolation or exposure to an unfamiliar adult male rat (Wiedenmayer *et al.*, 2000). Moreover, an increase in transcription of the immediate early gene, c-fos, has been demonstrated in the PAG of rats receiving electroacupuncture combined with a noxious stimulus to the tail compared to rats receiving the noxious stimulus alone (Zhou *et al.*, 1993).

Projections of the PAG to the pontine and medullary catecholamine cell groups, which in turn innervate the dorsal horn of the spinal cord (Bajic and Proudfit, 1999) as well as projections of the PAG to the hypothalamus (Behbehani *et al.*, 1988), mediate the antinociceptive capabilities of the PAG and underlie PAG-mediation of SIA.

4.1.5. Hypothalamus

Direct stimulation of the posterior hypothalamus produced a potent analgesic effect in the tail flick, pinch, and hot plate tests in an early study conducted by Rhodes and Liebeskind (1978) suggesting a role of the hypothalamus in the descending inhibitory pain pathway. In rats, direct stimulation of the preoptic and lateral regions of the hypothalamus produced an analgesic effect to facial heating (Cunningham *et al.*, 1986) and formalin injection (Lopez *et al.*, 1991), respectively.

In 1980, it was shown that lesion of the hypothalamic arcuate nucleus attenuated SIA in rats (Millan *et al.*, 1980a). Further studies with rats showed that lesions to the arcuate nucleus attenuated SIA four days after surgery, but could either attenuate or enhance SIA two weeks after surgery depending on the model of SIA (Kelsey *et al.*, 1986). Lesions of the hypothalamus also resulted in significantly less cold-water swim SIA in mice and rats (Tejwani and Richard, 1986; Truesdell and Bodnar, 1987). In another study, lesions to the paraventricular nucleus of the hypothalamus in rats had no effect on the analgesic response to restraint stress (Fuchs and Melzack, 1996). Taken together, the reports of the effect of lesions to the hypothalamus suggest distinct subregions play a role in mediating SIA.

Administration of renin and angiotensin directly into the hypothalamus of rats increased the latency to respond to noxious thermal stimuli co-administered with immobilization

stress, an effect attenuated with an antagonist to the angiotensin II receptor (Haulica *et al.*, 1986) (Table 2). Chemical blockade of the hypophyseal-adrenocortical system by direct administration of dexamethasone into the paraventricular nucleus of the hypothalamus of rats attenuated SIA suggesting a corticosteroid-dependent form of SIA mediated by the hypothalamus (Filaretov *et al.*, 1996). Moreoever, when oxytocin, a neurohormone synthesized in the hypothalamus during the stress response, was lacking in mice, SIA induced by a cold-water swim and restraint for 30 minutes was attenuated (Robinson *et al.*, 2002). Mice with a genetic disruption to orexin, which is also synthesized in the hypothalamus and plays a role in the transmission of pain, displayed a significant attenuation of SIA compared to wild-type mice (Watanabe *et al.*, 2005). The hypothalamic hormone vasopressin was not initially believed to play a role in SIA when an intraperitoneal injection of hypertonic saline was used as a stressor (Wright and Lincoln, 1985); however, a later study concluded that vasopressin mediated SIA with a food restriction stressor (Wideman *et al.*, 1996). Expression of mRNA for neurotensin, a peptide synthesized in the hypothalamus and involved in the regulation of luteinizing hormone and prolactin release, was shown to be increased in the lateral hypothalamus and medial preoptic area of rats following cold water stress suggesting that neurotensin is involved in the mediation of cold water swim SIA (Seta *et al.*, 2001). Furthermore, neither mice with a genetic disruption of neurotensin nor rats which received pharmacological administration of the neurotensin receptor antagonist SR 48692 displayed SIA when water avoidance was utilized as a stressor (Gui *et al.*, 2004). Thus, evidence suggests that an increase in activity in various subregions of the hypothalamus

occurs during SIA and that this region represents an important source of modulatory neuropeptides.

4.1.6. Brainstem

Bausbaum and Fields (1979) were able to show a map of neurons from the brainstem projecting to the spinal cord as part of the descending inhibitory pain pathway. An efferent anti-nociceptive projection of the meso-diencephalic junction to the spinal cord was also suggested to play a role during stimulation-produced analgesia (Peschanski and Mantyh, 1983). Rhodes and Liebeskind (1978) also demonstrated that stimulation of the pretectal region of the meso-diencephalic junction of the brainstem produced a potent analgesic effect in the tail-flick, pinch, and hot-plate tests. The hypothalamus can relay information to the PAG or the rostroventral medulla (RVM), both of which play a pivotal role in the modulation of nociception (Aimone *et al.*, 1988; Behbehani *et al.*, 1988; Cechetto and Saper, 1988). Neurons in the PAG relay information to brainstem regions such as the RVM, the parabrachial nucleus, and the nucleus tractus solitarius (Lewis *et al.*, 1987; Thurston and Randich, 1992; Yoshida *et al.*, 1997). The RVM inhibits efferent nociceptive transmission at the spinal cord (Fields and Heinricher, 1985; Heinricher *et al.*, 1989) through opioid dependent mechanisms (Heinricher *et al.*, 1994). The brainstem regions such as the RVM project to the dorsal horn of the spinal cord from which a relay to the primary afferent nerve terminals elicits the final phase of inhibition of nociception during SIA.

An increase in transcription of the immediate early gene, c-fos, was observed in the RVM of male rats receiving electroacupuncture to the tail compared to the pain control group (Zhou *et al.*, 1993) thus indicating an increase in the stimulation of this area during these conditions.

4.2. Spinal cord

Early studies utilising lesions and transections to the spinal cord suggested that descending inhibition of forepaw footshock SIA was mediated by the dorsolateral funiculus of the spinal cord whereas hindpaw footshock SIA was mediated by supraspinal or independent intraspinal pathways in rats (Watkins *et al.*, 1982; Watkins and Mayer, 1982). Mice with a genetic disruption of substance P, a peptide which is released into the dorsal horn of the spinal cord in response to a painful stimulus, displayed significantly less analgesia following forced swim stress coupled with the tail-flick test (De Felipe *et al.*, 1998). Neural cell adhesion molecules function to adhere lymphocytes to dorsal root ganglion neurons during inflammation (Cabot *et al.*, 1997). Administration of antibodies to neural cell adhesion molecules attenuated cold-water SIA to mechanical and thermal stimuli in rats (Hua *et al.*, 2006). Mice lacking oxytocin displayed significantly less analgesia during the tail-flick test following cold-swim or restraint stress (Robinson *et al.*, 2002). This study also showed that intrathecal delivery of the oxytocin receptor antagonist, dOVT, attenuated cold-water SIA. In a rat model of FCA, the number of c-fos labelled neurons in the spinal cord of rats expression FCA were significantly less than in rats expressing pain alone (Harris *et al.*, 1995). Furthermore, a significant reduction in

c-fos expression in the deep layers (IV-VI) of the spinal cord of rats which had received a hindpaw formalin injection following hemorrhagic shock was observed compared to the spinal cord of rats which had received formalin alone (Fukuda *et al.*, 2001) suggesting a decrease in neuronal activity in these regions during SIA compared to pain alone.

5. Neurochemistry of SIA

The differences in the mechanisms of descending facilitation versus inhibition of nociception lie mostly in the activation of receptor subtypes coupled to different intracellular signal transduction mechanisms (for review see Millan, 2002). Neurotransmitters or neuropeptides which may either facilitate or inhibit nociception include serotonin (5-hydroxytryptamine; 5-HT), noradrenaline, dopamine, dynorphin, acetylcholine, and nitric oxide (Akil *et al.*, 1972; Behbehani, 1982; Cruz and Basbaum, 1985; Hatakeyama *et al.*, 1996). There are, however, neurotransmitters which act predominantly to either facilitate or inhibit nociception. Neurotransmitters/neuropeptides which predominantly facilitate nociception include the excitatory amino acid glutamate, histamine, cholecystokinin, melanocortin, and prostaglandins (Faris *et al.*, 1983; Juan, 1981; Vrinten *et al.*, 2000; Xu *et al.*, 1995). Neurotransmitters/neuropeptides which predominantly inhibit nociception include GABA, glycine, vasopressin, oxytocin, adenosine, endogenous opioids, and endocannabinoids (Bernatzky *et al.*, 1983; Garcia-Arraras *et al.*, 1986; Le Bars *et al.*, 1980; Nakamura *et al.*, 1997; Sivam and Ho, 1983; Smith *et al.*, 1998; Zhang *et al.*, 1982). Brain regional alterations in levels of neurotransmitters unique to both facilitation or inhibition of nociception, the capacity of

these neurotransmitters to bind to their respective receptors, or differential binding to receptor subtypes can alter nociceptive transmission and mediate SIA (Figure 2).

5.1. Mediation and modulation of SIA by the opioid system

Studies of the mechanisms underlying SIA began with efforts to elucidate the role of endogenous opioid peptides and their corresponding receptors. A plethora of studies have confirmed the role of this system and attempted to identify the multiple brain regions which are involved in opioid signalling.

Morphine, which exerts its effects through activation of the opioid system, has been used as treatment for pain for centuries. In the 1970's, initial evidence of an endogenous opioid system was suggested when morphine produced an analgesic effect similar to that produced by stimulation of the PAG (Akil *et al.*, 1972). The discovery and characterisation of the opioid receptors shortly thereafter, along with endogenous opioids, confirmed this hypothesis (for review see Akil *et al.*, 1984). To date, three main opioid receptor families have been characterised, δ, κ, and μ. Endogenous opioids which have been identified and characterised include dynorphins, enkephalins, endorphins and endomorphins. All opioid receptors are metabotropic and ligand binding leads to the inhibition of adenylyl cyclase (Ho *et al.*, 1973; Naito and Kuriyama, 1973).

The opioid system has been demonstrated to mediate SIA (Akil *et al.*, 1986; Amit and Galina, 1986). Initial experiments which suggested a role for opioids showed that when

an antagonist for opioid receptors, naloxone, was administered, the analgesic effects of stimulation-produced analgesia were blocked (Akil *et al.*, 1976b). A study published shortly thereafter showed that naloxone increased the aversive response of rats exposed to painful electric shock (Fanselow and Bolles, 1979). With systemic or intra-cerebral administration of antagonists to the μ-, κ, or δ-opioid receptors, a complete attenuation of SIA and FCA in rats was observed (Akil *et al.*, 1976a; Fanselow *et al.*, 1989; Hart *et al.*, 1983). Moreover, administration of the enkephalinase inhibitor, thiorphan, potentiated both the peak effect and duration of SIA in rats, an effect blocked by administration of naloxone (Chipkin *et al.*, 1982; Greenberg and O'Keefe, 1982). SIA initiated by forced walking in rats administered formalin was also attenuated by administration of beta-EP-(1-27), an antagonist to the putative opioid epsilon receptor (Nakagawasai *et al.*, 1999). Although the immediate transient analgesic effect of placing a rat in a conditioned aversive environment was shown to be unaffected by naloxone administration, the enduring analgesia is blocked by naloxone (Harris and Westbrook, 1994). Moreover, opioid mediation of SIA has been shown to be dependent upon front paw footshock (Watkins *et al.*, 1982) and intermittent rather than continuous footshock stress (Lewis *et al.*, 1980). It was suggested that endogenous enkephalins mediated the tolerance to pain, but not the induction of analgesia in response to electroconvulsive shock (Urca *et al.*, 1983). In a model of FCA, a significant decrease in levels of beta-endorphin were measured in the pituitary and in the hypothalamus, but a significant increase in levels of beta-endorphin were measured in the plasma of rats exposed to conditioned stress compared to their non-stressed counterparts (Przewlocka *et al.*, 1990). Administration of naloxone to rats has also been shown to attenuate analgesia induced by olfactory and

contextual cues previously associated with morphine withdrawal (McNally and Akil, 2001). Human studies also showed that after conditioning to pair an auditory stimulus with mental arithmetic and white noise, re-exposure to the auditory stimulus resulted in an increase in pain tolerance and threshold and that the increase in pain tolerance was reduced by injection of naloxone (Flor *et al.*, 2002). Studies have shown that mice with a genetic deletion of the β-endorphin precursor molecule, proopiomelanocortin, do not express SIA whereas a genetic deletion of met-enkephalin does not affect the expression of SIA (Kieffer, 1999; Rubinstein *et al.*, 1996). These studies suggest that compared to met-enkephalin, β-endorphin plays a more prominent role in the expression of SIA. In addition, female transgenic mice lacking μ-, or δ-opioid receptors did not express SIA assessed in the hot plate test following forced swim stress (Contet *et al.*, 2006).

The endogenous opioid system has also been studied in the context of circadian variations in SIA which have been shown in mice to be related to fluctuations in endogenous opioid peptide release (Puglisi-Allegra *et al.*, 1982). Day-night rhythms have been demonstrated in naloxone-reversible, warm (opioid) and naloxone-insensitive, cold (non-opioid) swim SIA displayed by CF-1 mice, with maximum SIA observed at night (Kavaliers and Ossenkopp, 1988). Furthermore, a 30 min exposure to a 0.5 Hz rotating magnetic field reduced SIA with the effect being greater at night and in the opioid-sensitive model. Other work has shown that habituation to restraint SIA is more rapid at night than during the day although the magnitude of SIA did not vary with time of day (Miller, 1988). This study also demonstrated that morphine-induced analgesia in

the tail-flick test was potentiated by restraint in the nocturnal period but not in the diurnal period.

Early studies also suggested that the pituitary gland (MacLennan *et al.*, 1982; Millan *et al.*, 1980b) or central nervous system (Lewis *et al.*, 1981) synthesised opioids during SIA. Opioid receptors modulate the function of the ventrolateral PAG during FCA. Thus, administration of the μ-opioid receptor antagonist, naltrexone, into the ventrolateral PAG, attenuated the expression of FCA (Helmstetter and Landeira-Fernandez, 1990). Direct administration of naltrexone into the ventrolateral PAG also attenuated the analgesic effect of exposure of rat pups to an adult male coupled with thermal stimulation (Wiedenmayer and Barr, 2000). Decreases in Met-enkephalin-like immunoreactivity were observed in the mesolimbic area, striatum, hypothalamus, thalamus, prefrontal cortex, amygdaloid nuclei, and piriform cortex following SIA initiated by immobilization stress (Kurumaji *et al.*, 1987). Furthermore, SIA induced by social conflict was associated with a decrease in beta-endorphin-like immunoreactivity in the PAG (Kulling *et al.*, 1988). These authors also report that individual differences in baseline beta-endorphin-like immunoreactivity in the PAG correlate with the expression of high or low SIA (Kulling *et al.*, 1989). In a rat model of FCA, the acquisition of conditioned fear and the expression of FCA were both impaired with a unilateral injection of morphine into the amygdala (Good and Westbrook, 1995). Furthermore, FCA in rats was attenuated when synthesis of μ-opioid receptors in the rostral ventromedial medulla was blocked with direct infusion of antisense oligodeoxynucleotides (Foo and Helmstetter, 2000). A combination of opioid receptor antagonists for the μ- and κ-, μ- and δ-, or all three

subtypes delivered intrathecally attenuated SIA in rats (Watkins *et al.*, 1992). Another study suggested an involvement of spinal κ-opioid receptors in mediating footshock SIA (Menendez *et al.*, 1993). It has further been shown that G-proteins sensitive to pertussis toxin (Parolaro *et al.*, 1991) and G-protein inwardly rectifying potassium channels (Blednov *et al.*, 2003) are essential mediators of opioid-mediated SIA.

Evidence suggests that the antinociceptive effect of opioid receptor activation may, at least in part, be tied to the release of the inhibitory amino acid GABA and the excitatory amino acid glutamate (Ho *et al.*, 1976; Sherman and Gebhart, 1974b; for review see Christie *et al*., 2000). Opioid-induced antinociception is, for example, accompanied by altered release of GABA/glutamate and/or modulated by GABA/glutamate receptor ligands in a number of brain regions including the RVM (Gilbert and Franklin, 2002; Spinella *et al.*, 1996), PAG (Moreau and Fields, 1986; Stiller *et al.*, 1996), thalamus (Jia *et al*., 2004) and amygdala (Deyama *et al.*, 2007) as well as in the spinal cord (Nishiyama, 2000; Suh *et al.*, 2000). The following sections will discuss the role of GABA and glutamate in SIA.

5.2. GABA

Current knowledge suggests that γ-aminobutyric acid (GABA) is involved in over 40% of all inhibitory synaptic processing in the mammalian central nervous system (for review see Bowery and Smart, 2006). It is known that GABA modulates the function of the prefrontal cortex in the extinction of fear memories. Injection of the $GABA_A$ receptor

agonist, muscimol, into the infralimbic prefrontal cortex enhanced extinction of auditory fear conditioning (Akirav *et al.*, 2006). GABA has been shown to play a role in mediating anti-nociception mediated by both the opioid and endocannabinoid systems. For example, intravenous injection of muscimol attenuates the antinociceptive effects of morphine (Mantegazza *et al.*, 1979). Studies have shown localisation of cannabinoid type 1 (CB_1) receptors on the axon terminal of GABAergic interneurons (Katona *et al.*, 1999) and a role for GABA in mediating the antinociceptive effects of cannabinoids (Meng *et al.*, 1998; for review see Rea *et al.*, 2007).

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 (Tokuyama *et al.*, 1992). Cold-water swim SIA in mice was attenuated with intrathecal delivery of $GABA_A$ receptor antagonists, picrotoxin and biculline (Killian *et al.*, 1995). However, evidence on the precise roles of receptor subtypes is equivocal and dependent on the stressor employed (Houston *et al.*, 1997). Thus, further investigation into GABAergic mediation of unconditioned SIA is warranted but there is good evidence for GABAergic involvement in FCA. Systemic administration of the benzodiazepine, midazolam, which functions to enhance the inhibitory effect of GABA at the $GABA_A$ receptor, impaired FCA in a rat model which paired conditioning to a heated floor with the formalin test (Harris and Westbrook, 1996). Direct administration of benzodiazepines into the basolateral amygdala and the ventrolateral PAG also attenuated FCA in rats (Harris and Westbrook, 1995), supporting a role for

GABA in this brain regions in mediating FCA. A study by Helmstetter (1993) has also shown that direct administration of the benzodiazepine, diazepam, into the amygdala can attenuate FCA in rats. Attenuation of GABAergic inhibition of descending inhibitory pain pathway activity is the mechanism likely to underlie the attenuation of SIA by benzodiazepines.

5.3. Glutamate

Recent studies have shown an antinociceptive effect following blockade of N-methyl-D-aspartic acid (NMDA) receptors by direct infusion of MK-801 into the CA1 region of the hippocampus (Soleimannejad *et al.*, 2007). Glutamate has been shown to modulate nociceptive transmission in the PAG through opioid-dependent mechanisms (Sherman and Gebhart, 1974b).

Cox and Westbrook (1994) determined that the role of glutamate in SIA is in the acquisition and extinction of hypoalgesia. In their study, MK-801 was administered during the training phase, test phase, and both, to reveal that NMDA receptors do not alter the expression of FCA in rats, but do mediate the underlying acquisition and extinction of the conditioned response. However, another study demonstrated that bilateral infusion of the NMDA receptor antagonist d,l-2-amino-5-phosphonovaleric acid into the rat basolateral amygdala attenuated FCA when administered before the context and tone fear-retention tests (Lee *et al.*, 2001). In a forced walking SIA model, systemic injection of LY-235959, a competitive NMDA receptor antagonist, attenuated SIA in

formalin-injected mice aged 4 and 24 weeks, but not aged 48 weeks (Onodera *et al.*, 2001). Anti-nociception in the hot-plate test in mice exposed to a biting fly attack was attenuated in male, but not female mice, by the competitive NMDA receptor antagonist, NPC 1262 (Kavaliers *et al.*, 1998). Thus, a role for glutamate and glutamate receptors in SIA exists in an age- and sex-dependent manner.

5.4. Monoaminergic correlates of SIA

Catecholamines such as dopamine and noradrenaline and indolamines such as serotonin belong to a class of compounds called monoamines which play a major role in modulating brain function. Levels of monoamines are altered in response to nociceptive neurotransmission (for reviews see Millan, 1999, 2002) and monoaminergic systems have been shown to be involved in neurotransmission related to aversion (for review see Millan, 2003). It is not surprising, therefore, that there is also evidence for a role for monoamines at the point where nociception and aversion converge i.e. SIA.

A large number of dopaminergic neurons originate in the midbrain and innervate mesolimbic and mesocortical systems. In a rat SIA model combining tail-withdrawal to a noxious water heat with footshock, an increase in dopamine levels was measured in the hypothalamus and prefrontal cortex (Rosecrans *et al.*, 1986). In addition, increased levels of the dopamine metabolite 3,4-dihydroxyphenylacetic acid and the 3,4-dihydroxyphenylacetic acid:dopamine ratio in the PAG and reduced levels of dopamine

in the thalamus were measured in rats expressing FCA compared to fear-conditioned rats (Finn *et al.*, 2006).

Noradrenaline is released during stress partly from activation of the locus coeruleus (for review see Valentino and Van Bockstaele, 2008). Noradrenaline release is inhibited by activation of $GABA_A$, $GABA_B$, and opioid receptors (Fung and Fillenz, 1983; Gunne, 1959; Ishac *et al.*, 1996). Systemic administration of the α_2-adrenoceptor agonist clonidine was shown to potentiate cold-water swim SIA in rats (Bodnar *et al.*, 1983). Other workers reported elongated SIA in rats during the tail-flick test with systemic administration of the α_1-adrenoreceptor antagonist phenoxybenzamine (Snow *et al.*, 1982). Administration of noradrenaline blockers directly into the lumbrosacral cord resulted in attenuation of front paw footshock mediated SIA, but not hindpaw footshock mediated SIA or FCA (Watkins *et al.*, 1984).

Activation of serotonergic receptors can result in either hyperalgesia or analgesia depending on the receptor subtype activated (Sommer, 2006). The ratio of 5-HT metabolites to 5-HT was significantly higher in the frontal cortex in an SIA rat model of repeated footshocks followed by tail-flick latency in noxious thermal water (Rosecrans *et al.*, 1986). In another model of SIA involving open-arm induced antinociception in mice, administration of 5-HT(1A) receptor agonist 8-OH-DPAT produced biphasic responses as a low dose attenuated the analgesic response whereas a high dose resulted in enhancement (Nunes-de-Souza *et al.*, 2000).

Though the role of monoamines in descending modulation of pain is widely acknowledged, further studies using subtype selective agonists, antagonists and transgenic animals are needed to fully elucidate the exact mechanisms underlying monoaminergic regulation of SIA. In addition, interactions between the classical amine, amino acid and GABAergic neurotransmitter systems and the recently characterised endogenous cannabinoid (endocannabinoid) system are likely to be of importance and we will now review recent data supporting a role for the latter signalling system in SIA.

5.5. The role of the hypothalamo-pituitary-adrenal axis in SIA

The hypothalamo-pituitary-adrenal axis (HPA) is the major neuroendocrine arm of the stress response and influences other physiological processes such as digestion, energy storage and expenditure. The HPA axis has also been shown to play a role in the mediation of SIA (Filaretov *et al.*, 1996) – a concept that was briefly discussed in section 4.1.5. The first study to investigate the role of the HPA axis in SIA showed that hypophysectomized rats did not express cold-water swim SIA (Bodnar *et al.*, 1979). In another study, rats which had received chronic treatment of metyrapone, a drug known to increase levels of ACTH, expressed potentiated SIA in the tail flick and hot plate tests following cold-water swim (Mousa *et al.*, 1981). Studies also show that systemic injection of dexamethasone, an inhibitor of HPA axis function, or i.v. administration of hydrocortisone attenuates SIA in a rat model (Filaretov *et al.*, 1995; Mousa *et al.*, 1983). Mice which had been selectively bred to express HA showed a greater involvement of the HPA axis in the expression of swim-induced SIA as dexamethasone attenuated SIA in

HA mice but not in LA mice (Panocka *et al.*, 1987). Additional work has demonstrated that adrenalectomy enhances SIA in mice, an effect attenuated by dexamethasone (Marek *et al*., 1982). However, other forms of SIA, including an opioid-mediated form of SIA termed 'long-term analgesia' (MacLennan *et al*., 1982) and hemorrhagic shock-induced analgesia (Fukuda *et al*., 2007) are blocked by adrenalectomy and reinstated with corticosterone treatment prompting the conclusion that corticosterone plays a permissive role in SIA (MacLennan *et al*., 1982). Clearly, the HPA axis plays a role in the expression of SIA as indicated by these studies which have focused largely on unconditioned SIA. Finn *et al*. (2006), however, observed no differences in plasma corticosterone levels of rats expressing conditioned fear-induced suppression of formalin-evoked nociceptive behaviour, compared with non-fear-conditioned formalin-treated controls. To our knowledge, no studies have investigated the effects of circadian fluctuations in HPA axis activity on the expression of SIA.

5.6. Mediation and modulation of SIA by the endocannabinoid system

In 1965, Mechoulam and Gaoni identified Δ^9-tetrahydrocannabinol as the active principle of *Cannabis sativa* (Mechoulam and Gaoni, 1965). In the early 1990's, the cannabinoid receptors CB_1 and CB_2 were cloned and characterized (Matsuda *et al.*, 1990; Munro *et al.*, 1993). In addition, endogenous ligands for the cannabinoid receptors, termed endocannabinoids, were discovered around that time. These include anandamide, 2-arachidonoylglycerol (2-AG), noladin ether, virodhamine, and N-arachidonoyldopamine,

among others (Devane *et al.*, 1992; Hanus *et al.*, 2001; Huang *et al.*, 2002; Mechoulam *et al.*, 1995; Porter *et al.*, 2002; Sugiura *et al.*, 1995).

The modulation of brain function and synaptic efficacy by endocannabinoids is mediated by a process known as retrograde signalling. This is the process whereby a neurotransmitter or signalling messenger is released from the post-synaptic neuron to exert an effect pre-synaptically (Wilson and Nicoll, 2001). Endocannabinoid-mediated retrograde signalling has been observed or hypothesized to occur in stress-responsive brain regions including the hippocampus, amygdala, and in nociceptive regions such as the PAG, RVM, spinal trigeminal nucleus, and regions of the spinal cord (Jennings *et al.*, 2001; Katona *et al.*, 2001; Lichtman *et al.*, 1996; Meng *et al.*, 1998; Wilson and Nicoll, 2001). As the endogenous cannabinoids and their receptors were discovered and characterised, it became clear that they also mediate the processes involved in SIA.

The endocannabinoid system has been shown to modulate fear (Marsicano *et al.*, 2002), pain (Fride and Mechoulam, 1996), and SIA (Finn *et al.*, 2004; Hohmann *et al.*, 2005; Valverde *et al.*, 2000; for review see Vaughan, 2006). Mutant mice with an invalid CB_1 receptor gene displayed no antinociceptive effects following forced swimming in water at 34°C (Valverde *et al.*, 2000). Systemic administration of SR141716A (Rimonabant), a CB_1 receptor antagonist, attenuated FCA in a rat model combining contextually induced fear conditioning with the formalin test (Finn *et al.*, 2004). Studies have shown an increase in levels of anandamide and 2-AG in the basolateral amygdala of mice following expression of conditioned fear (Marsicano *et al.*, 2002) suggesting that the

endocannabinoid system in this brain region may mediate SIA. Recently, a study with an SIA rat model combining footshock with the tail-flick test in rats has shown that direct administration of SR141716A into the basolateral amygdala attenuated SIA (Connell *et al.*, 2006). However, we have found that administration of SR141716A into the right basolateral amygdala of rats did not alter anti-nociception in an FCA model, but did reduce the nociceptive response following a hindpaw formalin injection without fear-conditioning (Roche *et al.*, 2007). It appears therefore that the contribution of CB_1 receptors in the basolateral amygdala to SIA may differ depending on the nature of the stressor (i.e. unconditioned vs. conditioned) or indeed the nociceptive test (tail-flick vs. formalin). Injection of cannabinoid receptor agonists directly into the PAG significantly decreases aversive and nociceptive behaviours presumably by activation of the descending inhibitory pain pathway (Finn *et al.*, 2003) and injection of an antagonist for the CB_1 receptor directly into the dorsal PAG prevents non-opioid mediated SIA in rats (Hohmann *et al.*, 2005). The pharmacological inhibition of the enzymes involved in the degradation of anandamide and 2-AG, fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MGL), respectively, in the PAG of rats, resulted in enhancement of SIA via CB_1-dependent mechanisms (Hohmann *et al.*, 2005). Intrathecal administration of the MGL inhibitor URB602, or the FAAH inhibitors URB597 and arachidonoyl serotonin, enhanced footshock SIA in rats (Suplita *et al.*, 2006). However, this study also showed that intrathecal administration of the CB_1 receptor antagonist SR141716A did not attenuate SIA suggesting that endocannabinoids in the spinal cord were capable of modulating, but not mediating, SIA. Further evidence also suggests that

the endocannabinoid system and the neuropeptide cholecystokinin interact during the expression of SIA in mice (Kurrikoff *et al.*, 2008).

As discussed, administration of selective antagonists for both the CB_1 receptor (Finn *et al.*, 2004) and opioid receptors (Fanselow *et al.*, 1989) completely attenuates FCA in rats. Why then, does a proportion of FCA not remain when only one of these receptor types is selectively blocked? The most likely explanation would appear to be that the endogenous opioid and cannabinoid systems work together in a manner such that signaling through both opioid and CB_1 receptors is necessary for the expression of FCA. Indeed, there is good evidence for synergistic interactions between the opioid and cannabinoid receptor systems during modulation of nociceptive behaviour (Cichewicz and McCarthy, 2003). Moreover, it has been demonstrated that a physiological interaction between the opioid and cannabinoid systems is necessary for the development of opioid-mediated responses to stress (Valverde *et al.*, 2000). We have shown that inhibition of endocannabinoid catabolism with systemic administration of the FAAH inhibitor URB597 enhanced the expression of FCA in rats (Butler *et al.*, 2008). Furthermore, we showed that this enhancement is blocked by antagonists for the CB_1, CB_2, and opioid receptors, results which suggest an interaction between the opioid and endocannabinoid systems in the mediation of SIA.

6. Clinical implications of SIA and concluding remarks

Any thorough understanding of fundamental physiological processes such as pain requires an understanding of internal, evolutionarily developed modulating mechanisms. Studies of SIA have intertwined two highly important adaptive and survival responses in mammals. Furthermore, the revelation that pain can be naturally suppressed leads to the speculation that manipulation of the mechanisms of SIA could lead to therapies for pain disorders, hopefully without the need for the aversive aspect of SIA. On this point, studies have demonstrated that it is possible to modulate FCA without altering the duration of fear behaviours (Helmstetter and Fanselow, 1987a) and vice versa (Kinscheck *et al.*, 1984; Roche *et al.*, 2007). Thus, the conclusion has been drawn that fear is sufficient, but not necessary for conditional SIA (Harris and Westbrook, 1994). It may also be possible to utilize the expression of SIA as a predictor for development of psychological disorders. For example, the level of SIA sensitivity in abused women has been used as a marker for the future development of post-traumatic stress disorder (Nishith *et al.*, 2002). Furthermore, tests have shown that fibromyalgia (Guieu *et al.*, 1994; Lautenbacher and Rollman, 1997; Staud *et al.*, 2003; Staud *et al.*, 2004) and chronic headache (Pielsticker *et al.*, 2005) patients do not express DNIC to the same degree as healthy individuals and that DNIC is delayed in patients suffering from chronic fatigue syndrome (Meeus *et al.*, 2008). Thus, SIA- or DNIC-based tests aimed at investigating the functional integrity of endogenous analgesic systems may be useful as a

means to better understand the pathophysiology of these pain and anxiety disorders and also as potential diagnostic markers of these disorders.

It is now clear that pain is processed through multiple, interweaving receptor-mediated pathways utlilising the excitatory and inhibitory amino acids, monoaminergic, opioid, and endocannabinoid systems amongst others. While the nature of SIA from the pre-clinical perspective has become more complex, more opportunities have been uncovered for therapy of pain and stress/anxiety/depressive disorders (for review see Ford and Finn, 2008). These include monoaminergic, opioid, and endocannabinoids at the point of their synthesis, breakdown, or site of action. Most pharmacological agents aimed at treating pain are hindered by unwanted side effects such as gastrointestinal tract damage, constipation, addiction, respiratory depression. However, manipulations of the synthesis or breakdown of naturally synthesised chemicals which are clearly active during SIA, affords opportunities for the first time to treat pain without the unwanted side effects. Given the high incidence of co-morbidity of stress-related psychiatric disorders with persistent pain conditions (Twillman, 2007) and recent evidence for altered pain processing in patients with post-traumatic stress disorder (Geuze *et al.*, 2007), studies of the neurobiological mechanisms underpinning altered pain-related activity in the presence of aversive stimuli are, and will continue to be, of fundamental physiological and potential therapeutic significance.

Figure legends

Fig. 1. Mediation of stress-induced analgesia by activation of the descending inhibitory pain pathway. The descending inhibitory pain pathway originates in neurons in higher brain regions such as the cortex, hypothalamus, and amygdala – the amygdala being a region that is particularly activated by stress/fear. Neurons from these regions project on to the periaqueductal grey (PAG) and the rostroventral medulla (RVM) and finally to the dorsal horn of the spinal cord. Activation of this pathway elicits analgesia at the level of the dorsal horn by inhibiting the ascending transmission of nociceptive information.

Fig. 2. (A) Diagramatic representation of postulated synaptic neurochemistry underpinning regulation of stress-induced analgesia in brain regions such as the amygdala, periaqueductal grey, and rostroventral medulla. Fear/stress results in the release of endogenous opioids (eOpioids) from pre-synaptic neurons and endogenous cannabinoids (eCB) from post-synaptic neurons. The activation of the CB_1 or the μ-, κ-, or δ-opioid receptors on GABAergic interneurons inhibits the release of GABA and facilitates neurotransmission at glutamatergic synapses resulting in activation of the descending inhibitory pain pathway. (B) Neurochemistry of stress-induced analgesia in the spinal cord and periphery. Nociceptive transmission is mediated by release of neurotransmitters/neuropeptides, such as glutamate and substance P (SP) from the primary afferent nerve terminal. Activation of descending inhibitory pain pathway neurones results in the release of serotonin (5-HT), noradrenaline (NA), and eOpioids. Binding of 5-HT to inhibitory 5-HT receptors ($5\text{-}HT_R$) [$5\text{-}HT(1_{A,B,D,F}$ or 2_A) on the

primary afferent nerve terminal or 5-HT($1_{A,B,D}$ or 3) on the second order pain neuron], or NA and endogenous opioids to α_2-adrenoreceptor and μ-, κ-, δ-opioid receptors, respectively, on the primary afferent nerve terminal inhibits nociceptive transmission. Endogenous cannabinoids may also act via CB_1 and CB_2 receptors to modulate nociceptive transmission at the spinal level.

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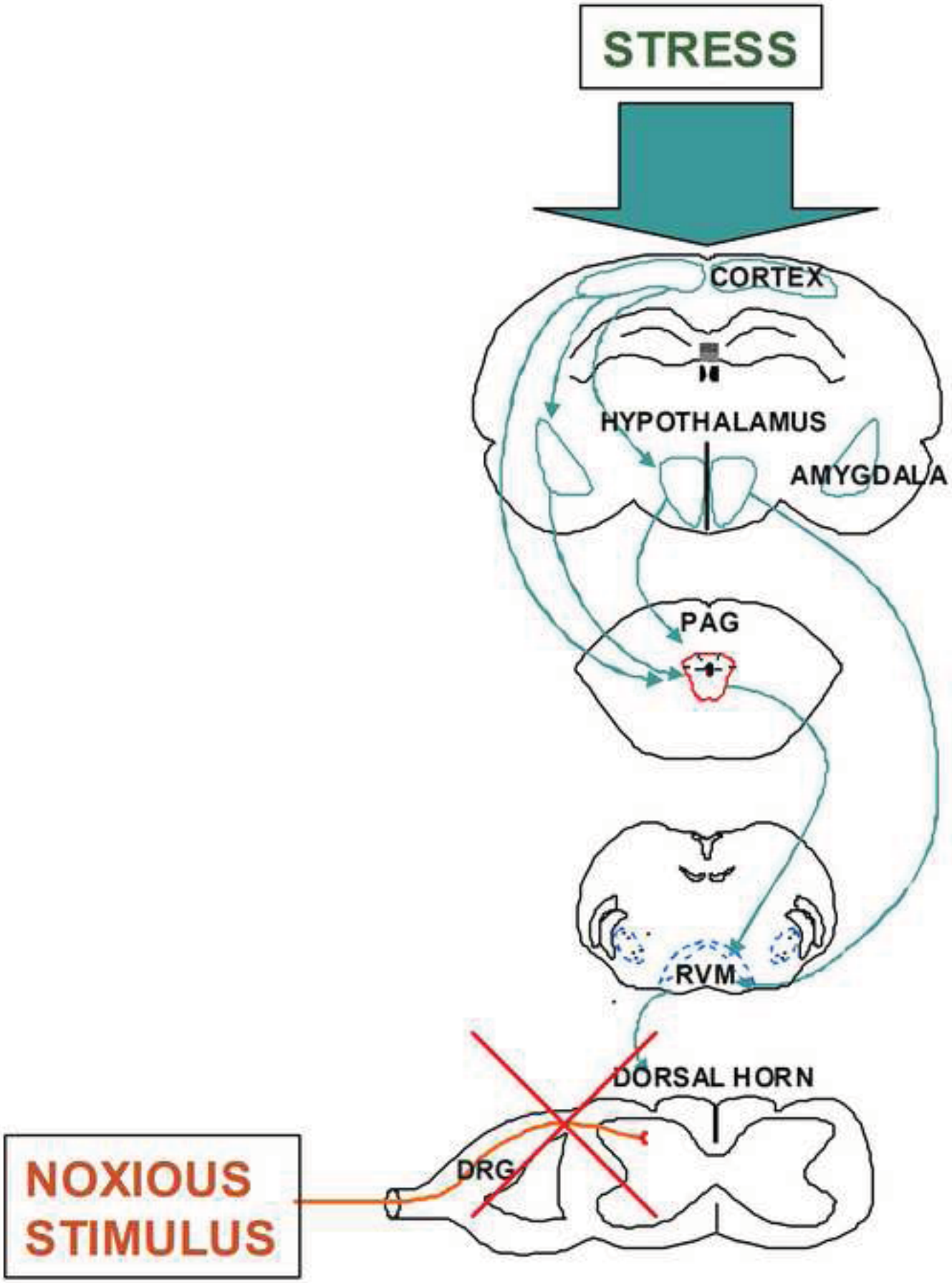

Figure 2

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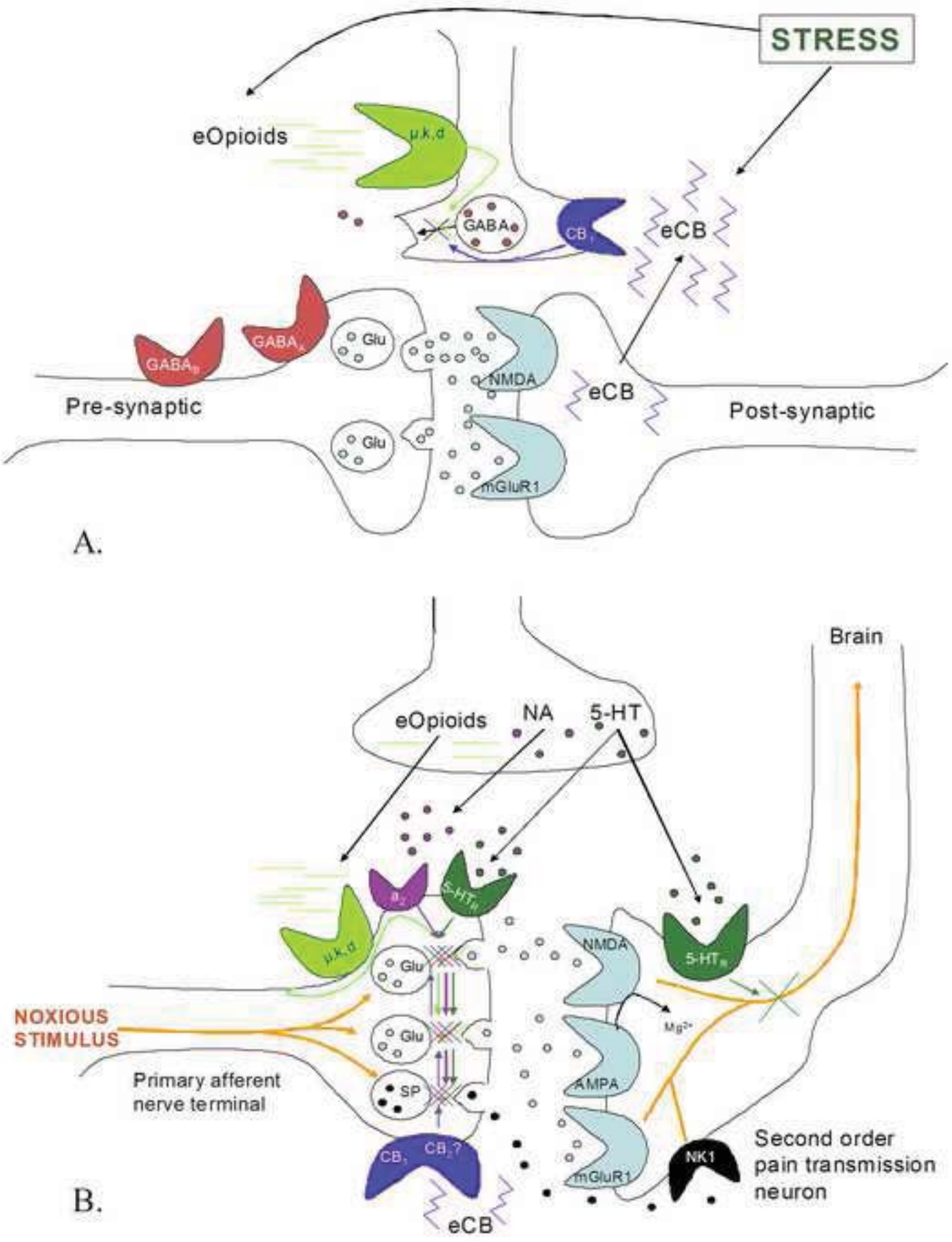

Table 1

Species	Painful stimuli	Stressful stimuli	References*
Rat	Formalin	Re-exposure to context associated with footshocks (CS)	(Helmstetter and Fanselow, 1987)
		Hemorrhagic shock	(Fukuda *et al*., 2001)
	Radiant heat	Footshocks (US)	(Akil *et al.*, 1976; Madden *et al.*, 1977)
		Re-exposure to context associated with footshocks (CS)	(Chance *et al.*, 1978; Hayes *et al.*, 1978)
		Continuous cold swim (US)	(Bodnar *et al.*, 1978a; Bodnar *et al.*, 1978b)
		Intermittent cold swim (US)	(Bodnar *et al.*, 1979)
		Intraperitoneal injection of hypertonic saline (US)	(Wright and Lincoln, 1985)
		Food restriction (US)	(Wideman *et al.*, 1996)
	Nitroglycerin	Restraint stress (US)	(Costa *et al.*, 2005)
Mouse	Formalin/Formic acid	Footshocks (US)	(Chesher and Chan, 1977)
	Radiant heat	Elevated plus maze (US)	(Lee and Rodgers, 1990)
		Exposure to predators (US)	(Kavaliers, 1988)
		Social isolation (US)	(Puglisi-Allegra and Oliverio, 1983)
		Defeat experience (US)	(Rodgers and Randall, 1987)
		Predator odor (US)	(Kavaliers *et al.*, 1997)
	Tail pinch	Communication box (US)	(Takahashi *et al.*, 1987)
	Insect bites	Social learning of fear to biting insects (CS)	(Kavaliers *et al.*, 2001)
	Attack by intruders	Social conflict (US)	(Rodgers and Hendrie, 1983)
Human	Intracutaneous electric current	Exposure to mental arithmetic plus noise (US) or re-exposure to green light previously paired to mental arithmetic plus noise (CS)	(Flor and Grusser, 1999)
		Re-exposure to auditory stimulus previously paired to mental arithmetic plus noise (CS)	(Flor *et al.*, 2002)
		Spider phobics exposed to spiders (CS)	(Janssen and Arntz, 1996)
	Radiant heat	Handshocks (US) or re-exposure to handshocks (CS)	(Rhudy and Meagher, 2000)
		Transcutaneous electrical nerve stimulation (US)	(Marchand *et al.*, 1991)
		War veterans with post-traumatic stress disorder viewing combat video (CS)	(van der Kolk *et al.*, 1989)
	Flexion reflex	Footshocks (US) or re-exposure to footshocks (CS)	(Willer *et al.*, 1981)
	Dental pain	Peripheral electrical stimulation (US)	(Abdulhameed *et al.*, 1989)
	Acute burn injuries	Virtual reality video game playing (US)	(Hoffman *et al.*, 2000)
	Tournequet ischemia	Transcutaneous electrical nerve stimulation (US)	(Walsh *et al.*, 1995)
	Lower back pain	Ice massage (US) or transcutaneous electrical stimulation (US)	(Melzack *et al.*, 1980)
	Tooth pulp stimulation	Hypnosis (US)	(Houle *et al.*, 1988)

Table 1: Summary of rodent and human models used to study the impact of stress on pain (CS, conditioned stimulus; US, unconditioned stimulus). * Every effort has been made to cite the original reference(s) that first described the model(s).

Table 2

Neuropeptide	Species	Experimental approach	Effect on SIA	References
Renin	Rat	Administered directly to hypothalamus	↑	(Haulica *et al.*, 1986)
Angiotensin	Rat	Administered directly to hypothalamus	↑	(Haulica *et al.*, 1986)
Neurotensin	Mouse	Genetic deletion of neurotensin	↓	(Gui *et al.*, 2004)
	Rat	Pharmacological blockade of neurotensin receptors with SR 48692	↓	(Gui *et al.*, 2004)
Oxytocin	Mouse	Genetic deletion of oxytocin	↓	(Robinson *et al.*, 2002)
Orexin	Mouse	Genetic deletion of orexin	↓	(Watanabe *et al.*, 2005)
Vasopressin	Rat	Comparison of vasopressin-containing rats versus vasopression-deficient rats	↑	(Wideman *et al.*, 1996)
Hypothalamo-pituitary-adrenal axis hormones	Rat	Administration of dexamethasone directly to the hypothalamus	↓	(Filaretov *et al.*, 1996)

Table 2: The role of hypothalamic neuropeptides in SIA.