Pain and relaxation (Review)

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Abstract. The modern notion of pain and its clinical management, along with its physiological origins, is of exceeding interest to both clinicians and basic science researchers. While much is known about the control of pain via non-steroidal anti-inflammatory medications or comparative exogenous analgesics, little is known about the interplay between pain perception and its relationship with catecholamine molecules. We believe that the perception of pain and the body's self-attempt to alleviate it utilizing conventional homeostatic mechanisms via endogenous opiate release is mediated by key catecholamines, and that this effect is further modulated by nitric oxide. We further propose a new paradigm which links pain, endogenous opiates, and the catecholamines in a unique robust fashion demonstrating a complex symbiotic signaling system.

Contents

1. Introduction

The notion of pain is often cited as the most frequent complaint made by patients visiting their primary care physicians. So much attention has been focused on pain that it has been recognized as the fifth vital sign, and is a key component in every patient's daily evaluation (1). While there is an abundance of literature with regard to the perception and sensation of pain, little is known about how its presence affects the body, and the mechanism by which these effects are mediated (2).

From a historical point of view, there has been substantial ambiguity about whether pain belongs to the domain of sensory physiology or to that of perceptual psychology. Fundamentally, this is simply a question of which explanatory scheme is best suited to dealing with the subjective experience that we call pain. For many years, the physiological/anatomical model dominated thinking, and pain was thought of as a sensory process with the primary goal of informing the organism of tissue damage. Early theorists believed that pain receptors detected tissue damage and generated action potentials along the spinothalamic tract as well as other pain specific pathways, where sensory input was organized and routed to numerous unspecified areas of the central nervous system (CNS). Such projections were lumped together under the broad category of 'pain centers' residing in the brain. The pain experience and its involved areas of the CNS are now recognized to be a much more complex phenomenon. It is believed that each pain receptor structure has its own unique activating stimulus and that these unique pain generating receptors transmit impulses that follow specific spinal tracts, and are routed through specific regions of the thalamus (3,4). Moreover, contemporary theorists stress that, as sensory information transmission alone, pain involves such wide-ranging effects as emotional arousal, motivational drive and cognition (2). As well as initiating processes with the sole purpose of acting to alleviate pain, such theorists take us into the realm of the endogenous opioid signaling molecules, and their numerous mediating molecules. Thus while the concept of pain has been difficult to explain and define, there is nonetheless a wealth of literature documenting the ability of opioid peptides and opiate alkaloids to ameliorate the sensation of pain. We examine these endogenous pathways more closely in this review.

2. Pain perception in general

We can loosely define pain as any stimulus which is either causing or on the verge of causing tissue damage, such as a needle about to penetrate the skin. Pain differs from other somatosensations in that the initial stimulus initiates a series of events within both the brain and spinal cord which can

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alter any future pain sensation (5). For example the pain of an initial prick with a needle is perceived as more painful than subsequent pricks. We surmise that this finding alludes to the endogenous opiate self-modifying system, discussed below. Furthermore, pain is a unique sensory experience in that it can be altered by past experiences, societal beliefs, and emotional states (6). These findings support the notion that pain is not purely a physiological event, but rather is mediated by psychological schemas as well (5,7).

Pain nociceptors (of various histological forms) respond to their respective stimuli, such as pressure, mechanical, or thermal. In addition, these nociceptors can be activated by varying molecules including catacholamines, bradykinen, histamine, cytokines, prostaglandins, as well as many of the other substances outlined in this report. It is the release of these substances in the peripheral blood, and/or tissues, which causes the sensation of pain during the inflammatory response. If the stimulus causes actual tissue damage, the above molecules act to further regulate the inflammatory response with vessel vasodilation initiating the inflammatory/clotting/bradykinen cascade (5). This strongly suggests a link to nitric oxide (NO) as the molecule chiefly responsible for vasodilation during inflammation, and released bradykinens as the cause of pain in this example. In addition, these nociceptors have several unique properties such as their ability to self-regulate and alter subsequent painful stimuli. This alteration could act to enhance the painful sensation resulting in hyperalgesia, as it is often noted clinically in diabetic peripheral neuropathy where exquisite pain is felt on palpation (5,8). The reverse scenario is also possible, endogenous opiates can be released via a descending corticospinal pathway leading to analgesia and decreased nociceptor sensitivity, essentially alleviating pain before it can even enter the CNS (5).

Recently, human white blood cells were shown to have the ability to make morphine, suggesting that their 'activation' may also contribute to peripheral pain perception (9). Moreover, the above marks the rationale for stimulation-induced analgesia, where by stimulating regions of the spinal cord we can induce dramatic reductions in pain by taking advantage of these descending opiate pathways. It is this endogenous system which allows for the relief of pain by 'classical' exogenous opiate administration, via homologous receptor sites (5,10).

3. Specific neural pathways involved in pain processing

The areas of the CNS involved in pain processing, which begin subsequent to thalamic routing and concurrent with routing to the primary sensory cortex, i.e., most notably the amygdala and the hippocampus, are areas classically involved in emotion and memory; critical functions of the so-called limbic system of the brain. Hence, it is no surprise that these two limbic areas are of great importance to pain regulation. Importantly, the central nucleus of the amygdala is most strongly modulated by dopamine (DA), norepinephrine (NE), epinephrine and serotonin (4,11). The basal nuclei receive moderately high inputs of DA, NE and serotonin (4,11), each of which has been demonstrated to exert their desired effect, in part, via NO (12-16).

We surmise that the centrally released NE exerts effects in the periphery by initially promoting a slight vasoconstriction of the peripheral artery during the amygdalar response to pain input as part of the limbic system's inherent mechanism to maintain homeostasis and decrease pain perception via descending spinal pathways resulting in endogenous opiate analgesia (12,13). This mechanism is indicated by a slight enhancement of sympathetic activity upon stimulation by a painful stimulus, and is immediately followed by the release of NO from peripheral endothelium, which mediates a concentration-dependent vasodilation (17), initiating the inflammatory process often coupled with pain. With regard to events centered on the palliation of pain both the hippocampus and the amygdala (particularly the lateral nucleus) contain high concentrations of receptors for the endocannabinoids as well (18). In fact, reports have found endogenous morphine within the structure of the hippocampus (14,19-21). In addition, this morphine may activate pleasure pathways via NO in rat brain hippocampus (21). Studies from our laboratory confirm the mediated release of NO from rat brain hippocampus and amygdala (14).

This information can further be used to understand some of the endogenous pain relief that occurs particularly after exposure to a series of painful stimuli, a mechanism that is found to have morphine-like properties and, perhaps, is mediated via these endocannabinoid and morphine-laden amygdalar pathways (14,16). Further credence to these findings stems from lesional data. Humans with amygdala lesions show a decrease in emotional tension and related pain thresholds (4,11). It has been postulated that endocannabinoids and endogenous morphine may act on the lateral nucleus to prevent the linkage of painful sensory stimuli prior to conscious processing, thus interfering with the perception of pain and painful stimuli (22).

The endocannabinoids are naturally occurring NO stimulating signaling molecules that are also constitutively expressed (23). Anandamide can also cause NO release from human immune cells, neural tissues and human vascular endothelial cells (24) and can initiate invertebrate immune cell constitutive NO synthase (cNOS)-derived NO (25). Enhanced cNOS activity would be a beneficial effect within the concept and time framework of the amygdalar ability to compensate for sensed pain and the subsequent analgesia that it induces. Thus, these signal molecules, especially endocannabinoid and opiate alkaloids (17,26,27), have the potential to alleviate pain (17,28).

As noted above, once individuals are exposed to painful stimuli such as a penetrating needle they experience peripheral vasodilation, warming of the skin (29-32) an increase in heart rate and a sense of agitation, all as a result of circulating catecholamines and/or NO (5). This is the function of the amygdala and related subcortical regions to aid in the relief of these pain states (3,4,27). In examining a potential mechanism for this relief, besides the overriding CNS output via the autonomic nervous system, peripheral neuro-vascular processes would appear to be important. We surmise that NO and its relation with prostaglandins are of fundamental importance in this response because of the increase in peripheral temperature, i.e., vasodilation, in the ensuing inflammatory response (29-32). Indeed this is precisely the pathway which

is inhibited with non-steroidal anti-inflammatory drugs (NSAIDS). Interestingly, nitrosative stress, mediated by involvement of the reactive nitrogen oxide species, N2O3, inhibits dopamine hydroxylase, inhibiting NE synthesis and contributing to the regulation of neurotransmission and vasodilation (17,33). This system may provide an autoregulatory mechanism involved in the neuronal control of peripheral vasomotor responses as they relate to pain control, where induction of a catecholamine inhibiting substance may autoregulate the vasomotor response in response to nitrosative stress [see (34) for the role of nitrosative stress in neuropathic pain].

4. The unique role of dopamine in pain

When we examine the role of the biogenic amines in chemical signaling, we often refer to the catecholamines as a general class. Recent studies have turned their attention chiefly to the role of dopamine in pain perception as well as its role in mediating opiate analgesia. It has long been known that the primary effect of the mu-receptor binding opiates comes from its ability to block the reuptake of dopamine, increasing its circulating half life (35). This unbound circulating dopamine is free to bind to the nucleus accumbens and other brain structures often refereed to reward pathways of the nervous system leading to the well-studied notion of physiologic dependence (5,35,36). This link has been the accepted paradigm for much of the past twenty years, recent reports however indicate that the excess dopamine does more than simply act as a byproduct of opiate-induced dependence, but rather is a key mediator in the actual reduction of pain (37). Indeed, recent reports have demonstrated that in addition to the classical pathway via dopamine reuptake inhibition, dopamine itself can be transformed via endogenous cellular enzymes, including CYP2D6, into morphine (9,38). Thus we are left with an extremely robust signaling system whereby endogenous morphine can be synthesized via endogenous dopamine, levels of which can further be influenced and/or modulated by endogenous morphine itself (9,38-40).

These findings have paved the way for recent understanding into the numerous observed *in vivo* findings when morphine is added to cell cultures; specifically, the ability of dopamine to affect immune system functioning (41). Depending on the environment and cell type, dopamine has activating and suppressive effects on an array of cytokines, such as interleukin-1, -6, tumor necrosis factor, and interferon (9). How these effects are mediated was previously unknown, however, this new paradigm suggests a potential role for morphine signaling in these processes. In addition to a direct metabolic link, there are alternative hypotheses regarding the interaction between dopamine and morphine. For example, dopamine may actually act via cell surface dopamine receptors, supported by the observation that dopamine receptor antagonists can block morphine-induced immunomodulation (37,41,42).

5. Specific involvement of catecholamines in pain

In normal healthy myocardium, any increase in oxygen demand or physiological stress to the body is met with significant coronary artery vasodilation, in an attempt to compensate for the oxygen deficit induced by circulating catecholamines and resulting stress-induced tachycardia (5,43). This effect is regulated by a series of endothelial involved vasodilators, which exert their dilatory effects via NO release (10,43). In healthy individuals, a balance is struck between the competing vasoconstriction α adrenergic systems resulting in a healthy patent vessel. In a dysfunctional vessel, there is increased catecholamine-induced vasoconstriction that can not be balanced due to damaged endothelium, leading to net vasoconstriction of the vessel (43). The resulting NO deficit is a possible regulator of ischemic pain via free radical formation (44) in a mechanism discussed below. In fact, dysregulation of this system may contribute to silent ischemia due to autonomic dysfunction in the diabetic patient (10).

A similar interaction of catecholamine and NO occurs in the setting of neuropathic pain, the precise etiology of which is unclear (8,32). It is believed to be the result of metabolic, ischemic, hereditary, compressive, traumatic, infections/immune-mediated events (8,32). Typically, the patient will present with paresthesias, and sensory deficits, and exquisite pain. It is believed that the result of this pain is mediated by the NO-mediated vasodilation response as part of the immune reaction to the damaged neuron (10,32,34). In some cases, the pain is caused by the binding of circulating catecholamines from the sympathetic nervous system (5,8,32). It is thought that the damaged sympathetic neurons become increasingly sensitive to norepinephrine from the post-ganglionic sympathetic terminal. In addition, cell bodies within the dorsal root ganglion also become hypersensitive to norepinephrine input. This hypersensitivity within the ganglionic chain is the basis for referred pain as well as the basis for sympathetic ganglionic blockade. These two examples together outline some of the more recognized interactions between circulating catecholamines, NO and the pain they mediate (10,32).

Additional illustrations of NO involvement in pain stem from the link between inflammation and bradykinin signaling processes. Bradykinin is a peptide that is produced and exerts its effects at the tissue site of injury or at any site of inflammation (5,36). In the periphery the actions of kinins include vasodilation, increased vascular permeability, the stimulation of immune cells, and stimulation of sensory neurons to induce pain (45). The mechanism for this pain induction is believed to be the result of NO free radical formation (10,44). Thus, it appears we have a theoretical framework in which to understand NO and catecholamine-induced pain. It is often the circulating catecholamines, which initiate a cascade of events leading to pain, as in the case of ischemic heart disease where the development of tachycardia increases oxygen demand (43). This is subsequently followed by NO-induced compensation either to increase oxygen supply or to act as an inflammatory mediator coupled to bradykinin. Finally, it is the resulting NO which breaks down into highly reactive free radical species which interact with the kinin system to modulate pain (10,44).

6. Pain perception as a homeostatic mechanism and the relaxation response

In general, pain is coupled with physiological stress, and when the body is exposed to these stressors it imparts

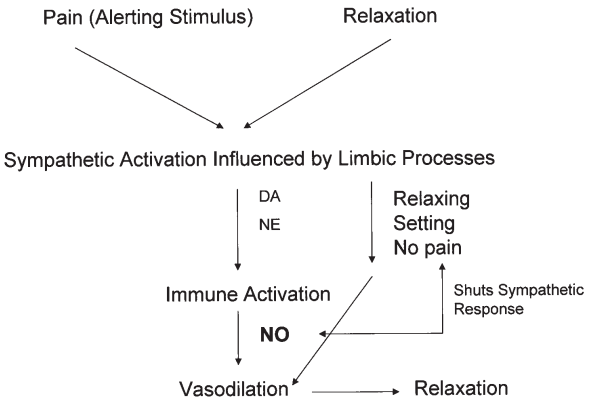

Figure 1. The relaxation response, in order to be activated, shares signaling pathways with excitatory and alerting phenomena, such as pain. The common alerting or excitatory components must emerge early in the process, so that it can be determined that the environment is appropriately relaxing and safe. Then, nitric oxide emerges to dampen the excitatory pathways and processes and promote relaxation (details of this signaling can be found in refs. 17,53,71,82,83).

negative effects on immunological, cardiovascular, and neurodegenerative diseases as well as neurological disorders, respectively (22,27,46-51). These reported systemic effects include alterations of immune function leading to impaired host humeral and cell mediated immunity, rendering the host susceptible to opportunistic infection. Cardiovascular effects include increased likelihood of having a cardiac ischemic event when compared with individuals lacking such stressors, as well as increased long-term propensity for vascular damage, e.g., due to impaired glucose tolerance due to cortisol excess. Neurological effects include increased propensity for degenerative diseases such as Alzheimer's and Parkinson's disease (47-49,52-57). The details of such effects are beyond the scope of this report but often involve damage via NO free radical formation (10,44,58,59; detailed mechanisms reviewed in refs. 27,46,48-51).

When the brain perceives a stimulus as painful, physiologic and behavioral responses are initiated, leading to homeostasis and adaptation, mitigating the event (as above). The goal of the body when confronted with pain and stress is to alleviate it, with the ultimate goal centered on organism survival (22,46). As a result of this ongoing adaptation mechanism given conditions of chronic pain, homeostatic loads can become overwhelmed and the body's ability to compensate can be permanently altered, and the overexposure to neural, endocrine, and immune pain mediators (see below) can have adverse effects on involved organ systems, leading to the onset or progression of diseases, due to immune system compromise or cardiovascular alterations (22,46-49). Currently, there are two processes that are recognized to play a major role in the stress response associated with pain, these processes have been thoroughly examined and their functions are well-known. They are chiefly the hypothalamic pituitary adrenal axis (HPA) and the sympathoadrenal medullary (SAM) system (60). More specifically, cortisol and norepinephrine are primarily responsible (61-65). Other molecules involved, e.g., melatonin (66) and anandamide (28), and the connection of NO with the pain response (16,28,65,66), as mentioned above, have also been detected.

The pain-associated stress response represents a group of common physiological and molecular pathways that are activated in situations that require behavioral adjustments. As these physiological changes play a role in pain-related disease processes (63-65), so does the relaxation response (Fig. 1). The relaxation response is defined by a set of integrated physiological mechanisms and adjustments that are elicited when a subject engages in a repetitive mental or physical activity and passively ignores distracting thoughts (28). These methods, such as hypnosis and music listening, have been shown to alter the perception of pain (67,68). Furthermore the physiological changes that occur include decreased oxygen consumption and carbon dioxide elimination (i.e., reduced metabolism), lowered heart rate, arterial blood pressure, and respiratory rate (68-71). These effects are chiefly mediated by the catecholamine interactions with endogenous opiates and the coupled constitutive NO release (70,72-74).

We surmise that the innate ability of relaxation to alter pain perception functions as a protective mechanism against excessive pain, antagonizing the potentially harmful effects of the pain and its associated stress (75,76) (Fig. 1). Furthermore, such findings lend further credence to the linkage between catecholamines, NO and pain, since it is via these molecules that the relaxation response exerts its effects. In addition, it has been demonstrated that sensitivity to NE can be reduced in chronic pain states and occurs via repeated stimulation within the dorsal root ganglion decreasing the resting membrane potential, thereby decreasing the sympathetic nervous system reactivity during painful stimuli (75,76). Moreover, serotonin and dopamine levels apparently are also elevated during the use of relaxation techniques (77-79). It therefore seems that the relaxation response has a role in pain palliation and that this effect is critically mediated by catecholamines and NO (52,80). This is especially true because of the emotional qualities that a pain stimulus may depend on, which involve limbic structures (15,16,71,81,82).

7. Conclusion

Our conclusion is two-fold. We demonstrate that pain regulation is mediated by a careful interplay between catecholamine molecules and further mediated by NO release. Furthermore, we propose that painful stimuli induce a series of homeostatic control mechanisms, which act in response to the stimulus, and appear to be mediated by a system of regulation involving NO as a neurotransmitter and as a locally acting hormone. Contingent on the preliminary vasoconstriction and depolarization of the membrane, vasodilation is mediated by the NO liberated from vasodilator nerves that activate guanylate cyclase in smooth muscle and produce cyclic GMP (cGMP). During this stage, NO and NE exist simultaneously. Due to the characteristics of NO, NE no longer mediates vasoconstriction; instead, NO activates guanylate cyclase, which produces vasodilation and relaxation under a depolarized membrane state. Hence, these two principle roles of the homeostasis exert their respective behaviors via NO. Furthermore, it is interesting that in the synthesis of morphine in animal tissues dopamine comes before morphine, allowing for potent stimulation followed by a rewarding calm.

In summary, we have discussed numerous mechanisms and neurochemical pathways with regard to the perception of painful stimuli, and we have shown a link between each of these complex pathways systems, as well as the use of NO as a major biochemical messenger. Moreover, throughout each of the aforementioned pathways, we have attempted to offer a possible relationship to catecholamine molecules, either as a chief regulatory messenger system or as an inducer or regulator of NO.

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