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Review Articles

The psychophisiology of pain: a literature review

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Abstract
The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage". The sensory aspect of pain is associated with the transmission of the painful impulse called nociception. The emotional aspect, on the other hand, is related to the behavioral responses to pain. Pain warns us about some impending danger, protecting our organism and indicating limits. Besides inducing physical anomalies, pain can interfere with the psychological equilibrium of the individual. This literature review about the psychophysiology of pain aims to elucidate the ways of action of this phenomenon and its relation with behavioral alterations. The management of pain is based on its etiology, physiopathology and repercussions. In addition to the use of analgesics and adjuvants, the therapy should include non-pharmacological tools such as physiotherapy and rehabilitation as well as psychotherapeutic procedures.

Keywords
Pain, nociception, psychophysiology, perception

Introduction

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage". The sensation of pain plays a physiological role, warning us about threats to the physical integrity of our body (CHAPMAN et al., 1999). In this sense, pain is a clinically important symptom not only for detecting and evaluating disease but also for inducing caution and consequently limiting possible damage (MILLAN, 1999; WOOLF, 2000; ALMEIDA et al., 2004).

It has already been well established that pain is a complex experience not only involving the transduction of a noxious stimulus but also the cognitive and emotional process occurring in the brain (CHAPMAN et al., 1999; JULIUS et al., 2001; ALMEIDA et al., 2004).

The phenomenon pain involves thus two components: the first is the sensory-discriminative component providing information on location, modality and intensity of stimuli; the second is the affective-motivational component, being responsible for the behavioral responses to pain. This component is characterized by defensive behavior such as the withdrawal reflex or fight-flight reaction (MELZACK, 1975; ALMEIDA et al., 2004).

The sensory component is related to the mechanism, through which the painful impulse created by actual or potential tissue damage reaches the central nervous system (CNS). This mechanism is called nociception (MERSKEY et al., 1979). The affective-motivational component on the other hand is related to the characteristics of the individual as refers to his/her mood state, to the symbolic meaning attributed to the sensory phenomenon and to cultural and emotional aspects (TEIXEIRA et al., 2001).

Pain is important because it warns us about impending danger, protecting our body and indicating the limits that should not be transgressed (DIAS, 2007).

Although being a warning sign used by our body to signal injury or danger, pain interferes with the internal equilibrium of the individual and its relations with others (PIRES, 2007).

Current research seeks to elucidate the physiological and emotional mechanisms of pain aiming to discover new pharmaceuticals capable of alleviating of even eliminating the pain process.

This review about aims at elucidating the ways of action of this phenomenon and its relation with behavioral alterations. The article is based on information obtained in different data bases: Pubmed, Sciencedirect, Medline, Lillacs, Scielo, and Capes. The terms used in this search were among others: pain, physiology of pain, psychophysiology of pain, mechanisms of pain, and preference was given to more recent articles. For definitions of a more generalized nature, we also used some books of the field of physiology and pharmacology.

Physiology of pain

Types of pain

According to OLIVEIRA (1979), pain is a warning sign used by the CNS to signal an assault against our body and its physical integrity. This warning sign unleashes a series of psychological and withdrawal reflexes for preserving our organism.

Pain is a protective response of the body alerting the individual to impending or actual tissue damage, inducing coordinate reflex and behavioral responses aimed at keeping the tissue damage as far as possible within limits (WOOLF et al., 1999). This kind of pain is classified as acute pain (TEIXEIRA et al., 2001). On the other hand, the pain persisting beyond the time normally associated with tissue injury and not any more characterized as a protective response to some impending threat is classified as chronic pain, generated by small impulses produced by abnormal neural activity (MELZACK et al., 1999).

Chronic pain can result from the continuation of an organic disease or persist after the recovery from the disease or injury. When associated with an organic disease, this pain will subside when the basic disorder is removed. Chronic pain is generally not well localized, tends to be severe, continuous or recurring and can be divided into the categories nociceptive, neuropathic and psychogenic (MERSKEY et al., 1994; SMITH et al., 1986; FÜRST, 1999).

Nociceptive pain is the result of persistent thermal, chemical or mechanical stimulation of nociceptors. When activated, they transmit pain signals to the brain causing the pain observed in individuals suffering from cancer or Herpes zoster among others (MILLAN, 1999).

Neuropathic pain, on the other hand, is defined by the IASP as being caused by an injury or dysfunction of the central or peripheral nervous system. Such dysfunction can be provoked by compression, transsection, infiltration, ischemia, metabolic injury of neural cell bodies or a combination of all these factors (GALLUZZI, 2007) and is responsible for phantom pain and the pain associated with diabetes melittus and Parkinson's disease (BOWSHER, 1999).

Psychogenic pain is a pain disorder, in which the painful sensation if mainly generated by psychological factors. This kind of pain is observed in disorders such as depression and anxiety (FURST, 1999; MERSKEY, 1986).

The perception of pain

The perception of pain occurs in two distinct stages. The first, called nociception, refers to the transduction of a noxious stimulus to the CNS through specialized receptors, the nociceptors (FURST, 1999). The second stage refers to the elaborated processing of this nociceptive signal leading to conscious perception of pain (BALDO, 1999).

The pain process begins in the nociceptors, which are morphologically differentiated receptors present in

the free afferent nerve endings (FURST, 1999). They are sensitized by a potentially noxious stimulus, this is, a stimulus exceeding a determinate level considered normal (innocuous stimulus) (BURGESS et al., 1967; MILLAN, 1999).

The nociceptors, localized in the distal portion of the afferent sensory neurons (first-order neurons), are widely distributed in the skin, vessels, muscles, joints and viscera (JULIUS et al., 2001). They are divided into three classes: mechanoceptors, sensitive to intense mechanic stimuli; thermoceptors, sensitive to thermal stimuli (over 45°C) and polymodal nociceptors, sensitive to mechanical, thermal and chemical stimuli (TEIXEIRA et al., 1994; BESSON, 1999). These receptors exhibit as a basic feature lack of accommodation and increased sensitivity to continuous stimulation (CHEN et al., 1996; LIEBESKIND, 1976).

The stimulation of the nociceptors, which can occur through change of temperature (thermal stimulus), osmotic difference or tissue distension (mechanic stimulus), hypoxia or tissue injury followed by inflammation (chemical stimulus), promotes a local release of chemical mediators like bradykinine, protons, hystamine, serotonin, arachidonic acid metabolites, ATP, adenosine, cytokines, amino acids, acetylcholine, among others. These mediators interact with specific nociceptors propagating the noxious impulse by altering the membrane permeability of the nervous fiber generating the action potential (JULIUS et al., 2001; GRIFFIS et al., 2006). There also exist afferent fibers that do not sense normal stimuli, called "silent" or "sleeping" nociceptors. When stimulated by inflammatory mediators however or after administration of pro-inflammatory agents, these silent nociceptors present spontaneous activity or are sensitized and respond to sensory stimuli (JULIUS et al., 2001).

The nociceptors transmit the painful stimuli to the spinal cord via three kinds of afferent sensory fibers: A-beta fibers, which are myelinated fibers with more than 10 μm in diameter, conduction velocity of 30-100 m/s and that respond to tactile stimuli; A-delta fibers, which are myelinated fibers with an average diameter of 2-6 μm, conduction velocity of 12-30m/s, responsible for fast conduction of painful stimuli; and C fibers, which are unmyelinated, with a diameter varying between 0.4-1.2 μm and conduction velocity of 0.5-2 m/s, responsible for slow transmission of painful stimuli. The C fibers constitute the greater part of sensory fibers (FURST, 1999; GRUBB, 1998; SHELLEY et al., 1994).

The A-delta fibers are known to be responsible for the transmission of the "initial pain", which is quick and sharp, while the C fibers transmit the secondary, slow and dull pain (JULIUS et al., 2001).

The peripheral nociceptors and their dorsal root ganglion cell bodies are located in the terminals of the first-order sensory neurons. They transmit the nociceptive information to the neurons of the dorsal horn of the spinal cord. The principal neurotransmitters responsible for the transmission of the nervous impulse from the first-order afferent fibers to the neurons of the dorsal horn are substance P and glutamate (CALNE et al., 1996; CODERRE et al., 1992). This process depends on the calcium and sodium channels, the first-mentioned being the main regulators of neurotransmitter release (HILL, 2001).

The dorsal horn is divided into six laminae, according to the characteristics of its neurons. The nociceptive neurons are located in laminae I, II and V (ALMEIDA et al., 2004).

After direct or indirect interaction with first-order afferent neurons of the dorsal horn, the second-order neuronal axons form afferent tracts that transmit the nociceptive impulses to structures of the brainstem and the midbrain, including thalamus, *periaqueductal gray, reticular formation, amygdaloid complex and hypothalamus among others* (ALMEIDA et al., 2004).

The transmission of nociceptive information to the higher centers occurs through the anterolateral tract of the spinal cord. The principal pathways of pain in the CNS are the spinothalamic, reticulospinal and spinomesencephalic tracts (CAILLIET, 1999; MILLAN, 1999).

The reticulospinal tract, also known as slow conductor, is phylogenetically old and runs medially through the brainstem. It is linked to the ascendant reticular activating system (ARAS) *and to the ventral periaqueductal gray and transmits diffuse projections to the thalamus, cortex and structures of the limbic system. The spinothalamic tract or fast conductor is phylogenetically younger and follows the lateral margin of the brain stem. It transmits projections to the ventrobasal thalamus and from there to the sensory cortex* (RUSSO et al., 1998).

Another important pathway is the spinomesencephalic tract, which ends in some regions of the midbrain that include the mesencephalic reticular formation and the periaqueductal gray. The latter region maintains reciprocal connections with the limbic system via hypothalamus (BALDO, 1999).

Although in man the axons of the anterolateral tract cells cross over to the other side of the spinal cord, there is a small but significant ipsilateral component that may explain the return of the pain, the so-called phantom limb pain, in patients that suffered section of this tract. The projection pathways of pain show great divergences of terminations in the brainstem providing neural support to behavioral activation and alert, induced by the painful stimulus. Many pain-activated anterolateral fibers terminate in the midbrain roof plate (BASBAUM et al., 2002).

A great number of neurotransmitters and modulators involved in the transmission of the nociceptive signal from the medulla to the higher centers are being discovered. However, electrophysiological studies suggest glutamate and other excitatory amino acids acting via ionotropic receptors and metabotropic receptors for glutamate to be involved in the transmission of the nociceptive information from the spinothalamic tract to the thalamus, and from the spinomesencephalic tract to the vPAG (AZKUE et al., 1997; ERICSSON et al., 1995; JENSEN et al., 1992; SALT et al., 1996).

The thalamus plays a fundamental role in the integration of the painful impulse. Third–order neurons transmit impulses from the thalamus to the brain cortex, where the noxious stimulus is processed resulting in the perception of pain (FÜRST, 1999).

The descendent pathways running from the midbrain through the rostral ventromedial medulla to the dorsal horn of the spinal cord follow a course diametrically opposite to the ascendant pathways. They have inhibitory and modulatory effect upon distal structures, particularly upon the posterior cord of the medulla, where the balance between nociceptive and non-nociceptive stimuli can control the transmission of painful information to higher centers (MELZACK et al., 1965; GUTSTEIN et al., 1998).

The gate control theory of pain

The most widely accepted theory for explaining pain modulation is the gate control theory put forward by Ronald MELZACK e Patrick WALL in 1965. The theory is based on the idea that the transmission of impulses from the peripheral afferent fibers to the thalamus through the transmission neurons in the dorsal horn of the spinal cord is modulated. The spinal cord works as a regulating station for pain transmission. The perception of pain is thus the balance between sensory stimulation and an intensive central control.

The afferent nociceptive fibers transmit the painful impulse to the thalamus through the transmissors situated in the dorsal horn of the spinal cord constituting the transmission pathway, which is controlled by the neurons of the gelatinous substance (GS). Descendant inhibiting neurons or nonnocicpetive afferent influx activate the neurons of the GS, which in turn inhibit the pain transmission cells, hampering the transmission of the painful impulse to the higher centers. Stimulation of the C fibers, on the other hand, inhibits the inhibitory neurons of the GS, allowing the transmission of the painful impulse to the thalamus, with this modulating the transmission of the painful impulse to the higher centers (YAKSH et al., 1994).

The gate control theory does not only approach the sensory aspect of pain but also the psychological variables and their influence upon pain sensation. This occurs through cognitive evaluation and through information from earlier experiences stored in superior cortical regions linked to the motivational component. Alterations in this component can modify the reaction to pain even in absence of changes in its sensory component, principally in chronic pain (BROTON et al., 1982).

Central pain control

It is known that painful stimuli are subject to central modulatory effects and that in situations of physical stress or great concentration painful stimuli are tolerated. This is why the existence of a central physiological pain control system was suggested. This system can also be activated by stimuli such as disease, cognitive behavior or even by pain itself (URBAN et al., 1999).

The analgesic process occurs through stimulation of different loci such as the *ventral periaqueductal gray, the locus coeruleus* and the rostral ventromedial medulla. Direct projections connect the pre-frontal and insular cortex, hypothalamus, amygdala and the brainstem to *the ventral periaqueductal gray. The latter connects to the* rostral ventromedial medulla, which in turn projects to the dorsal horn of the spinal cord. The rostral ventromedial medulla is the greatest source of brainstem neurons for the dorsal horn, mainly for laminae I, II and V (FIELDS et al., 1999; URBAN et al., 1999). This way, stimulation of the ventral *periaqueductal gray provokes excitation of the* rostral ventromedial medulla neurons, which in turn release neurotransmissors like serotonin and encephalin. These neurotransmissors inhibit the nociceoptive responses of the neurons of the dorsal horn, reducing the responses to the painful stimuli (BASBAUM et al., 2000).

There are also the noradrenergic neurons found in the locus coeruleus, whose main antagonist is noradrenaline (FRITSCHY et al.,1987; CLARK et al., 1991), which has an inhibitory effect upon pain transmission in the dorsal horn (BELCHER et al., 1978).

Intrathecal administration of noradrenaline produces antinociceptive effects proving its participation in pain control (YAKSH et al., 1979; REDDY et al., 1980). Furthermore, noradrenaline antagonists reduce the antinocieption produced by the stimulation of the supraspinal cord (BARBARO et al.,1985; JONES et al., 1986).

Pain receptors and ligands

The principal pain receptors are the opiates, serotonergics, noradrenergics and vallinoids.

The opiate receptors are mainly found in the limbic system and in the *ventral periaqueductal gray, but also in the peripheral nervous system* (HARLAN et al., 2002). *Opiate receptors can be observed in areas correlated with pain perception (*laminae I, II and V), modulation of the affective behavior (amygdala, hypocampus, *locus coeruleus* and córtex), and with the regulation of the autonomous nervous system and neurodegenerative functions (olfactory bulb and hypothalamus) (ARVIDSSON et al., 1995a,b).

Studies demonstrate that the analgesic effect of the opiates is due to their property to directly inhibit the ascendant transmission of nociceptive information from the dorsal horn of the spinal cord and to activate the pain control circuits that descend from the midbrain through the rostral ventromedial medulla to the dorsal horn of the spinal cord. The opiate peptides and their receptors are found in all these descending pain pathways (GUTSTEIN et al., 1998).

The types of opiate receptors are μ (mu), κ (kappa) and Δ (delta). They differ in their affinity to endogenous opiate ligands and also to exogenous opiate drugs. The main opiate ligands are: encephaline, selective for delta receptors, dynorphin, selective for kappa receptors; and endorphin, binding with high affinity to delta and mu receptors and with low affinity to the kappa receptors (LORD et al., 1977). All of them are coupled to G protein

and inhibit adenylate cyclase, thus reducing the intracellular cyclic adenosin monophosphate content (cAMP) (DHAWAN et al., 1996).

The encephalins, which are present in the interneurons of the gelatinous substance (GS) of the posterior spinal cord, for example, present antinociceptive effects that seem to be activated by the pre- and post synaptic actions to inhibit the release of substance P and to reduce the activities of the cells projecting from the spinal cord to the higher centers of the CNS (HOFFMAN et al., 2003).

As refers to the serotoninergic receptors, these are 5-HT_{1A} metabotropic receptors whose principal ligand is serotonin (5-hydroxytryptamine), mainly present in the nucleus raphe magnus (HOYER et al., 1994). This nucleus in particular plays a pivotal role in integrating nociception and affective information through projections descending to the spinal cord and projections ascending to the brain cortex (YAARI et al., 1985).

Serotonin is involved in different levels of nociception regulation. Release of this neurotransmissor inhibits the transmission of the painful impulse to the CNS, inducing analgesia. The serotoninergic nuclei of the dorsal raphe, under influence of the encephaligernic pathways, modulate the activity of the *nucleus accumbens*, amygdala and habenula (YAARI et al., 1985; MICO et al., 2006).

The vaniloid receptors are non-selective cation channels, which are activated by heat (temperatures over 43ºC), low pH, endogenous lipids like anandamide and lipoxigenase products. They are distributed over afferent first-order neurons, dorsal root ganglia and the entire brain (CATERINA et al.,1997).

Recent evidence demonstrated that the vaniloid receptors, stimulated by endocarabinoids or by capsaicine in the ventral periaqueductal gray, induce analgesia. This analgesic effect is associated with increased release of glutamate and activation of cells of the rostral ventromedial medulla. Activation of the descendent nocicpetive pathway through stimulation of this receptor in the ventral periaqueductal gray may be a new strategy for producing analgesia (PALAZZO et al., 2008; MAIONE et al., 2006; JIA et al., 2005).

The motivational aspects of pain

Pain involves an emotional aspect that contributes to enhancing the sensation of pain depending on the subjective experience of the individual (MELZACK et al., 1999). In certain situations the intensity and duration of pain is disproportional to the aggressive stimulus (LOESER et al., 1999; MILLAN, 1999), demonstrating the participation of the emotional component in the painful sensation.

The sensory stimuli of pain are related to defensive behaviors. It is already known that, anatomically, there is a superposition of neural substrates, which are connected to pain/fear behavior in the midbrain roof plate (BASBAUM et al., 2002). There is also evidence that fear inhibits pain in humans (RHUDY et al., 2004).

BOLLES and FANSELOW (1980) proposed a model for explaining the fear/pain behavior called perceptual-defensive-recuperative (PFR) model. This model shows that fear and pain generate distinct behaviors.

Two behaviors can be activated following a painful injury: the recuperative behavior, responsible for the recovery of the individual, or the defensive behavior, which inhibits recuperative behavior and pain and promotes environmental perception and defense (BOLLES et al., 1980). In other words, pain activates endogenous opiate mechanisms that inhibit the medial pain system because the expression of this system can compete or even contradict with the defensive behavior (RHUDY et al., 2004).

The PDR model can be divided into three phases: perceptive, defensive and recuperative (BOLLES et al., 1980). The perceptive phase is a brief phase, during which the stimulus is detected and learned. This learned stimulus serves as a signal for eliciting defensive behaviors.

The role of this learning is to make the conditioned stimulus induce the expectation of the nonconditioned stimulus. In case the nonconditioned stimulus occurs again, its real characteristics are confronted with the expected characteristics. Any discrepancy between the perceived and expected stimuli is corrected by the learning system in order to avoid wrong expectations in the future. The expectation of the nonconditiones stimulus elicits the defensive behavior. Thus, the conversion of nociception into pain involves factors such as previous experience, cognitive aspects and the cultural and social context (BROTON et al., 1982) generating different responses to pain in different individuals and in different moments (MELZACK, 1975; MELZACK et al., 1994; 1971; BOLLES et al., 1980).

The defensive phase is the moment in which the reaction to the stimulus occurs. This reaction involves increase of fear and reduction of pain, activating the endogenous analgesic system and generating defensive behavior. The recuperative phase, on the other hand, is characterized by the cure of the injury and activation of the affective-motivational component of pain due to tissue damage and inhibition of any other type of motivation. This phase is marked by recuperative behavior, i.e. care and rest (BOLLES et al.,1980).

Psychological alterations due to pain

Pain sensation is subjective and personal, since each individual senses pain according to his/her early-life experiences (MERSKEY et al., 1979). This is the reason for the subjectivity in the interpretation of the painful experience and its emotional and sensory character. Besides inducing physical anomalies, pain also interferes with the psychological equilibrium of the individual (TEIXEIRA, 2006).

Chronic pain can lead to important psychological and social dysfunctions. Such dysfunctions can be caused by neurotransmitter deficit, alterations in the receptors, biological rhythm disorders, neuroendocrine or immu-

nological anomalies and/or genetic factors (TEIXEIRA, 2006).

Individuals suffering from chronic pain are more susceptible to depression than normal people (SULLIVAN et al., 1992). About 30% to 54% of patients suffering from chronic pain such as headache, neck pain, lower back pain, chest, abdominal, pelvic and limb pain present frequently depressive disorders (BANKS et al.,1996; VON KNORRING et al., 1983), generally requiring specialized treatment (WARD, 1990).

On the other hand, individuals with depression or anxiety are more vulnerable to pain. A considerable number of individuals with depression, especially when accompanied by anxiety, are complaining of pain (WÖRTZ, 1994). Individuals with depression complain of chronic pain in different parts of the body in absence of lesions that could justify this pain (MAGNI et al., 1990).

Situations like stress, fear, anxiety and the duration of pain interfere with the activation of the opiate system, which is involved in the modulation of analgesia (BROTON et al., 1982). Nociceptive neuromodulators are activated in case of intense pain or stress (TERMAN et al., 1984).

Depression and anxiety interact in the perception of pain via inhibitory or facilitating mechanisms (MEYER, 1985). The noradrenergic and serotoninergic pathways are involved in the mechanisms of anxiety and depression as well as in the central pain control system. The interaction between inhibitory and excitatory units, the emotional state, individual characteristics, prior and present experiences, organic or functional disorders and environmental conditions can interfere with the transmission of the nociceptive information to nerve centers that participate in the perception of pain or reflex reactions to pain. Psychological stress turns pain more intense or less tolerable (TEIXEIRA, 2006).

Pain management

The management of pain should be based on its etiology, physiopathology and repercussions, removing the cause and controlling the pain sensation using analgesics, adjuvants and anti-inflammatory medications. As a matter of fact, most analgesics available on the market have anti-inflammatory characteristics (MENDELL et al., 2003).

In addition, the therapy should include non-pharmacological tools such as physiotherapy and rehabilitation as well as psychotherapeutic procedures (CATALANO et al., 2004). In special situations, anesthetic and neurosurgical procedures can be valuable tools for alleviating certain cases of resistant pain (TEIXEIRA, 1988).

Pain management is aimed at alleviating the pain and reducing the use of medications, functional reintegration of the patient and improvement of his/her quality of life. In cases of acute pain, the interventions seek eliminating the discomfort, basically through removing its cause, use of analgesic drugs and through simple physical and behavioral medicine procedures (CANDELETTI et al., 1985).

The treatment of chronic pain involves symptomatic measures, specially use of adjuvants, physiotherapy and social reintegration. The prescription of medicaments is generally the first strategy adopted in both acute and chronic pain management (AMANO et al., 1986).

The opiates are widely used in the management of cancer-related and acute pain. However, some clinicians still resist using these analgesics mainly due to their concern with side-effects such as drug-induced respiratory depression and with the lack of knowledge about individual physiological responses such as tolerance and physical and psychological dependence (McQUAY, 1999).

Although nociceptive pain generally responds to opioid medication, neuropathic pain is frequently resistant to this medication and may require increasing doses. The opiates are thus more efficient in the management of nocicpetive pain than in the management of neuropathic pain (FIELDS, 1988; COLOMBO et al., 2006).

The use of a variety of antidepressant medications is associated with pain reduction, an effect that is independent of the mood-enhancing qualities of these drugs. This pain relief is a consequence of a great variety of actions of the antidepressants on the neuroregulatory mechanisms associated with pain perception and transmission (McCLEANE, 2008). The use of tricyclic antidepressants is efficient in providing pain relief (SINDRUP et al., 1999; O'MALLEY et al., 2000). Some of these antidepressants are selective serotonin reuptake inhibitors but there are more efficient drugs that inhibit not only serotonin but also noradrenalin reuptake (JANN et al., 2007).

Final remarks

The present survey shows the complexity of the pain process, including not only the sensory – anatomic-functional – dimension (depending on the transmission pathways) but also the motivational-affective aspect, with highly subjective responses in different individuals. The management of pain is thus difficult, as illustrated by the non-exclusive use of analgesics. A better understanding of this complex process will open new perspectives for controlling this phenomenon.

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