

Anatomy and Physiology of Pain

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ABSTRACT

Pain is a sensory experience and distinct from nociception, which refers to the neural mechanisms involved in detecting tissue damage. This article reviews nociceptive mechanisms and how these relate to pain sensation. The emphasis is on recent advances in our understanding of nociceptive mechanisms, including transduction at the peripheral nociceptor terminal, ascending pathways, and the cortical role in pain. Plasticity in nociceptive systems and a new role for descending systems in pain facilitation are also discussed.

KEYWORDS: Nociceptive mechanisms, transduction, cortex, plasticity, modulation

Objectives: Upon completion of this article, the reader should be able to: (1) review nociceptive mechanisms in primary afferents, ascending pathways, and cortex; and (2) recognize how CNS plasticity and descending facilitation might contribute to chronic pain states.

Pain is an unpleasant bodily sensory experience commonly produced by processes that damage, or are capable of damaging, bodily tissue. This idea of pain emphasizes that pain is a sensory experience and that it is distinct from *nociception*, which refers to the neural mechanisms involved in detecting tissue damage. The need for this distinction arose from the recognition that pain does not necessarily bear a direct relationship to tissue damage. A given damaging stimulus may or may not give rise to a sensation of pain. Conversely, there are conditions in which pain occurs without any demonstrable damage to tissue. This definition also stresses that pain has an important motivational component, an aspect of unpleasantness or suffering. This aversive quality can be rated and often separated from the sensory-discriminative component of the sensation, which is revealed in judgments about intensity, quality, and location.

This article focuses on nociceptive mechanisms and how these relate to pain sensation. The emphasis is

on some recent advances in our understanding of these mechanisms, and the reader is referred to texts by Fields¹ and Wall and Melzack² for a comprehensive review of the field.

TRANSDUCTION AT THE PRIMARY AFFERENT TERMINAL

Primary afferent nociceptors have two tasks. The first is to transduce a damaging or potentially damaging stimulus, whether mechanical, thermal, or chemical, into the code used by the nervous system, electrical potentials. The second task of the primary afferents is to transmit that information into the central nervous system for processing. The primary afferent itself is the sensory transducer, and our understanding of the molecular mechanisms through which damage to tissue results in activation of the primary afferent nociceptors has expanded dramatically over the last decade.^{3,4}

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Adequate stimuli for a nociceptor may include intense mechanical or thermal stimuli or chemical irritants. Mechanical nociceptors possess channels that are gated by mechanical deformation of the membrane and thus respond directly to mechanical stimuli. Thermal sensitivity (intense heat or cold) is thought by at least some investigators to be associated with expression of receptors in the transient receptor potential (TRP) family, including the vanilloid and related receptors (VR1 and VRL-1) and the cold- and menthol-sensitive receptor CMR1.⁵

The majority of nociceptive afferents are activated by the myriad of chemical mediators that are released or synthesized when tissue is damaged or inflamed. These include chemonociceptors, which respond only to chemical stimuli, and polymodal nociceptors, which respond to mechanical and/or thermal inputs as well as chemical stimuli. Some of the constituents of this "chemical soup" are known to activate nociceptors directly and to induce pain when applied to human volunteers. Other elements of the soup by themselves do not activate the afferents but induce sensitization, causing the afferents to be more responsive to other inputs (Fig. 1). Surprisingly large numbers of afferents seem to be unresponsive even to very intense stimulation under most normal conditions but begin to respond to mechanical and heat stimuli once "awakened" by these sensitizing mediators. Primary afferent sensitization is considered a major factor in enhanced pain following injury or inflammation.

VR1, the recently cloned vanilloid receptor, is activated by capsaicin, the pungent ingredient of chili peppers. This receptor belongs to the TRP receptor family and is located on terminals of many small-diameter afferents. The endogenous ligand is as yet unknown, and candidate ligands include anandamide and lipoxygenase products. VR1 and a closely related receptor, VRL-1, may transduce heat as well, as noted previously. Other chemical mediators released from damaged cells include adenosine triphosphate (ATP) and acetylcholine, which activate afferents through P2X purinergic receptors and nicotinic receptors,

respectively. ATP also sensitizes nociceptors, through an action at the P2Y purinergic receptor. Protons act through acid-sensing ion channels (ASICs) and/or the vanilloid receptor, VR1. Trypsin and tryptase, ligands of proteinase-activated receptor 2, produce nociceptive behaviors and thermal but not mechanical hyperalgesia in rats. Activation of this receptor thus presumably both activates and sensitizes nociceptors.⁶ Bradykinin is synthesized from a plasma precursor. Bradykinin is also known to activate afferents as well as sensitizing them, enhancing their responses to heat and lowering the response threshold. One particularly interesting suggestion is that this thermal sensitization allows the afferent to be activated by normal body temperature, a property that would clearly give rise to increased pain in inflamed tissue.⁷ The proinflammatory prostaglandins are probably the most important of the substances that sensitize nociceptors without directly evoking excitation. Prostaglandin E₂ (PGE₂) and PGI₂ are formed in inflamed tissue and bind to prostanoid receptors on the primary afferent terminals.

CENTRAL PROCESSING OF NOCICEPTIVE INFORMATION

Our understanding of the central neural mechanisms of pain sensation has increased substantially. Primary afferent nociceptors terminate in the superficial dorsal horn and deeper in lamina V. Nociceptive neurons, including some that are activated only by noxious stimulation and others that code stimulus intensity over a range from innocuous through noxious, are concentrated in both areas. A broad framework, in which a crossed spinothalamic projection ascending in the anterolateral quadrant serves as a "labeled line" for sensations of pain (and temperature), can be traced to clinical and experimental observations of the late 19th and early 20th centuries. Until recently, a role for cortical structures in pain sensation was often discounted (see Craig⁸ for an in-depth historical review). In contrast, current thinking emphasizes the importance of several parallel ascending

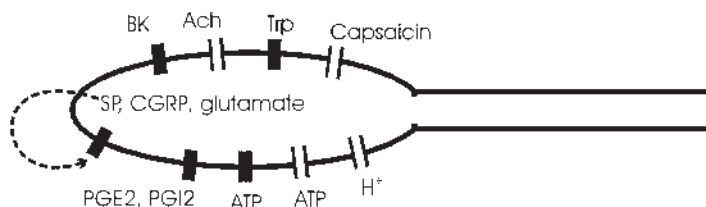


Figure 1 Terminals of the primary afferent nociceptors respond to mechanical and thermal stimuli as well as to a host of chemical mediators. Capsaicin, protons, ATP, and acetylcholine (Ach) act on ligand-gated cation channels to depolarize the terminal. Bradykinin (BK) acts on a G protein-coupled receptor to activate and sensitize the terminal. Trypsin (Trp) and tryptase also activate G protein-coupled receptors. Prostaglandins (PGE₂ and PGI₂) are formed by the actions of cyclooxygenase and act on prostanoid receptors to sensitize the terminal to other inputs. Substance P (SP), calcitonin gene-related peptide (CGRP), and glutamate are released from the terminal and contribute to neurogenic inflammation.

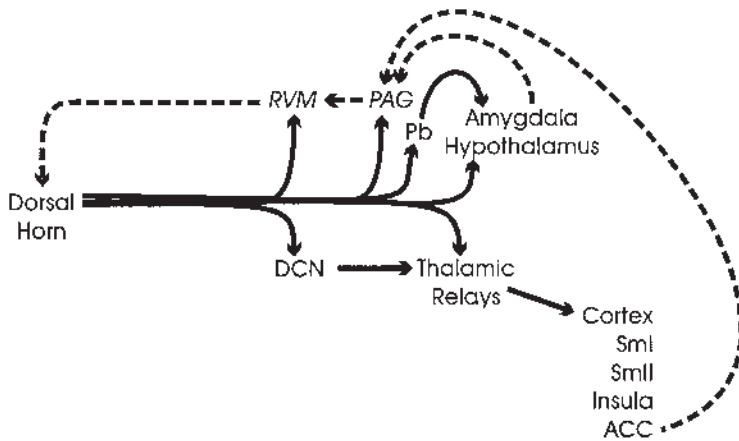


Figure 2 Distributed processing of nociceptive information and recurrent activation of modulatory systems. This simplified diagram shows multiple parallel nociceptive pathways ascending through as part of the anterolateral system and dorsal columns (solid lines). A projection through the dorsal columns appears to be particularly important in visceral pain, and the dorsal column nuclei relay visceral information to thalamus. In addition to connections to medial and lateral thalamus, the anterolateral system includes spinoparabrachial and spinothalamic systems. Spinoreticular and spinomesencephalic systems provide a means through which ascending information can influence the brainstem pain-modulating systems (dotted lines) via a short recurrent loop. Higher centers, including anterior cingulate cortex, amygdala, and hypothalamus, also project massively into the PAG and provide a substrate for limbic control of descending modulation. ACC, anterior cingulate cortex; DCN, dorsal column nuclei; PAG, periaqueductal gray; Pb, parabrachial complex; RVM, rostral ventromedial medulla; Sml and SmlI, primary and secondary somatosensory cortex.

pathways and emphasizes distributed processing at supraspinal levels, including cortex (Fig. 2).

PARALLEL ASCENDING PATHWAYS

An essential role for pathways ascending through the anterolateral quadrant is supported by several complementary lines of evidence. Many dorsal horn neurons projecting through the anterolateral system respond differentially or selectively to noxious stimulation. Direct electrical stimulation of the anterolateral white matter can give rise to pain sensation in humans, and the stimulation parameters required to produce this sensation parallel those required to activate nociceptive dorsal horn neurons. Finally, transection of the anterolateral quadrant can produce contralateral analgesia and thermesthesia below the level of the lesion, at least for a period of time. The evident functional importance of axons traveling in the anterolateral quadrant provided an impetus for anatomical definition of these pathways and their targets. These are now known to include not only the spinothalamic, spinoreticular, and spinomesencephalic systems identified in classical degeneration studies but also direct projections to the parabrachial complex and to the hypothalamus, amygdala, and other limbic and striatal forebrain structures.⁹⁻¹¹

Even if one considers only the spinothalamic pathway, targets include ventroposterolateral nucleus (trigeminal input is to ventroposteromedial nucleus) and ventral posterior inferior, ventral medial posterior (VMpo), central lateral, parafascicular, and medial dorsal nuclei. The functional significance of this spinothalamic divergence is as yet unclear, as physiological and behavioral studies lag anatomical findings. Craig and colleagues¹² have focused attention on the VMpo, which

they find is well developed only in primates. Their anatomical studies demonstrate a dense, topographically organized projection from lamina I of the dorsal horn to VMpo. VMpo neurons recorded in macaque are almost exclusively nociceptive or thermoreceptive. These authors also highlight the significance of a projection from the VMpo to the insular cortex, which has consistently been shown to be activated in association with pain sensation in imaging studies in humans (see later). However, the existence of VMpo as a distinct cytoarchitectural entity has been disputed,¹³ and other authors stress that lamina I is not the exclusive spinothalamic relay for nociceptive information. Neurons in lamina V and the deep dorsal horn similarly respond to noxious input and project to thalamic nuclei, including the ventroposterolateral nucleus (VPL). Nociceptive neurons, although not numerous, can be identified in VPL and its chief cortical targets, primary and secondary somatosensory cortex.

Another important supraspinal target of the anterolateral system is the parabrachial complex. The lateral parabrachial region receives a substantial projection from nociceptive neurons in lamina I. Lamina I spinoparabrachial neurons are known to be predominantly nociceptive, as are the majority of parabrachial neurons in the region targeted by the lamina I projection. These neurons in turn project primarily to amygdala and hypothalamus. These patterns of nociceptive responsiveness and connectivity suggest that the parabrachial area plays an important role in the motivational component of pain sensation and/or autonomic and endocrine responses to noxious stimulation. Neurons in the internal lateral parabrachial nucleus also respond to noxious stimulation. However, in contrast to the lateral parabrachial region, nociceptive input to the internal lateral parabrachial

nucleus derives from the deep dorsal horn (laminae V and VI), and neurons in the internal lateral nucleus send their axons to medial thalamus, predominantly to the paracentral nucleus. Thus, at least in rat, nociceptive information from the deep dorsal horn may be transmitted through medial thalamus to prefrontal and anterior cingulate cortex through a relay in the internal lateral parabrachial nucleus.¹⁴

A startling finding is the recognition that nociceptive information is conveyed through the dorsal columns to the dorsal column nuclei. Westlund, Al-Chaer, and colleagues¹⁵ have provided evidence that axons ascending in the dorsal column play an important role in visceral pain, especially from pelvic organs. The impetus for their work was a case report in which a midline myelotomy at T10 relieved pain due to cancer of the colon for a period of months. Electrophysiological experiments in rats showed that the responses of VPL thalamus neurons to colorectal distention were dramatically reduced by dorsal column lesions at T10, whereas responses to cutaneous stimuli were spared. Behavioral studies confirmed the importance of the dorsal column pathway in a rat model of pancreatitis. Anatomical tracing studies demonstrated a postsynaptic dorsal column pathway originating around the central canal (lamina X), with the greatest concentration of projecting neurons at more caudal levels. Although not as well studied as the dorsal horn, lamina X is known to receive a substantial input from small-diameter primary afferents and includes many nociceptive neurons. It thus seems that the dorsal columns, classically viewed as mediating fine tactile discrimination and proprioception, also contribute to visceral nociception, most notably from pelvic structures. The implications of these findings for understanding the pain-reducing effects of dorsal column stimulation have not yet been explored.

CORTICAL NETWORKS

The absence of robust impairment of pain sensation after lesions of somatosensory cortex and the failure of electrical stimulation to elicit sensations of pain in awake humans formed the basis for the classic view that pain, unlike other sensory systems, did not require cortical processing.⁸ This notion of subcortical processing was attractive in part because it was consistent with an idea that pain was a "primitive" sensation. This state of affairs was not, however, entirely satisfying for several reasons. Although there was apparently no cortical "pain center" that could be ablated to eliminate pain, several case reports indicated altered pain responses following various cortical lesions. Experimental work in animals also identified nociresponsive neurons in somatosensory cortex.^{16,17} Scientific interest in cortical processing important for pain was thus rekindled with the advent of imaging techniques showing parallel activation of cor-

tical regions in awake human experimental subjects in response to stimulation that produced a sensation of pain. These studies focused attention on primary and secondary somatosensory cortex, insula, and anterior cingulate cortex (Fig. 2), all of which show reasonably robust activation in functional neuroimaging studies using positron emission tomography or functional magnetic resonance imaging (see Peyron et al¹⁸ and Schnitzler and Ploner¹⁹ for reviews).

What is the role of each of these four regions of cortex in pain? In a particularly interesting and ingenious series of studies, the Montreal group has attempted to link primary somatosensory cortex and the anterior cingulate cortex with the sensory discriminative and motivational aspects of pain, respectively. Hypnosis was used to modulate selectively either perceived pain intensity or unpleasantness. When the subjects received instructions to modulate unpleasantness, the resulting altered ratings of unpleasantness showed a good correlation with regional cerebral blood flow (rCBF) in anterior cingulate cortex. Activation of somatosensory cortex was unchanged. In contrast, when a second group of subjects was instructed to modulate intensity, variations in perceived intensity were correlated with variations in rCBF in primary somatosensory cortex but not anterior cingulate cortex. Although these data could be interpreted as pointing to a specific role for the different regions in different aspects of pain, it should be noted that perceived unpleasantness covaried with perceived intensity when subjects were instructed to modulate intensity. Yet, there was no change in activation in the anterior cingulate cortex under these conditions. Thus, although there does seem to be a closer link of the sensory aspect of pain with primary somatosensory cortex and of the motivational aspect with the anterior cingulate cortex, it seems unlikely that the different cortical areas will prove to function as independent "centers" mediating different aspects of pain experience.²⁰

One of the obvious predictions derived from the initial neuroimaging studies was that clinical pain states would be associated with increased activity in the same regions activated by acute stimuli in experimental subjects. However, this turned out not to be the case. Probably the most significant finding from the still relatively small number of studies in patients with pain is that persistent pain states are associated with a decrease in activation, with most reliable changes in thalamus. Moreover, therapeutic stimulation (e.g., thalamus or motor cortex) is reported to enhance activity in at least some of the same regions activated by acute noxious stimulation.²¹⁻²³ It is assumed that this apparently paradoxical effect reflects some kind of "normalization" of a system that is somehow out of balance. Once again, it is apparent that there is not a simple one-to-one relationship between sensation and activity in a cortical pain center. Rather, multiple pathways ascend from the

spinal cord to targets in brainstem, thalamus, and forebrain. These areas probably process different aspects of the stimulus and interact in a dynamic fashion to give rise to the complex sensation that we call pain.

PLASTICITY IN NOCICEPTIVE PATHWAYS

Nociceptive circuits exhibit remarkable plasticity following injury to tissue or to the nervous system itself. This plasticity in nociceptive processing is manifest in persisting tenderness and hypersensitivity that can be manifest as a decrease in threshold (“allodynia,” in which normally innocuous stimuli such as light touch are perceived as painful) and an increased sensation in response to stimuli that normally elicit pain (“hyperalgesia”).

Sensitization of the primary afferent nociceptors is generally agreed to be the proximal mechanism for hyperalgesia in injured and inflamed tissue (see earlier discussion of primary afferent sensitization). Afferents innervating injured regions exhibit enhanced sensitivity and altered expression of molecular components of signal transduction and transmission. This results in an increase in afferent input to the dorsal horn, which in turn triggers functional modifications of the circuitry within the dorsal horn and at higher levels. This can further facilitate and maintain the increased pain sensation at the injured site and surrounding tissues even in the absence of continued input from the periphery. The alterations in dorsal horn and supraspinal processing sites are referred to as central sensitization. It is generally thought that central sensitization is particularly important for expansion of hyperalgesia to tissue surrounding the area of injury, the so-called secondary hyperalgesia.^{24–26}

INTRINSIC MODULATORY SYSTEMS

The idea that modulation of pain processing is a separable function of the central nervous system is now well supported.²⁷ The best known and probably functionally most significant central pain modulating system has critical links in the midbrain periaqueductal gray (PAG) and rostral ventromedial medulla (RVM; see Fig. 2). Electrical stimulation or focal application of neuroexcitant agents at either site produces a behaviorally measurable antinociception in animals, and PAG stimulation can produce analgesia in humans. This antinociception is due at least in part to a suppression of nociceptive processing at the level of the dorsal horn. The RVM projects to the dorsal horn via the dorsolateral funiculus, and the inhibitory output neurons are a class of neurons called off-cells.²⁸ A subset of the RVM outflow contains serotonin, although the role of RVM serotonergic neurons in pain modulation and their physiological properties are at present a matter of some dispute.^{29,30} The PAG itself has only a sparse projection to the dorsal

horn, and its effects on nociceptive processing are relayed through the RVM (see Heinricher³¹ and Heinricher and McGaraughty³² for reviews). Both the PAG and RVM project to pontine regions containing noradrenergic cell groups, which constitute another descending pathway paralleling that from the RVM.³³ Activation of this pathway produces an α_2 receptor-mediated antinociception.³⁴

The PAG is densely interconnected with limbic and forebrain structures including hypothalamus, preoptic area, amygdala, and orbitofrontal cortex. These connections provide an anatomical substrate for the influence of higher psychological variables such as stress, fear, attention, and learning on pain responses and presumably mediate the analgesic effects of deep brain stimulation in forebrain areas linked to the PAG. Physiological recruitment of the PAG-RVM axis (i.e., recruitment by means other than electrical stimulation or pharmacological treatment such as opioid analgesics) is generally part of an integrated defense response to an external threat (such as a predator or a learned predictor of environmental danger) or to interoceptive insults (such as deep tissue injury). Defense responses require integration of autonomic, endocrine, and behavioral responses (e.g., immobility or escape behavior) as well as nociceptive modulation to allow the organism to cope appropriately.^{35,36} Consistent with this idea of coordinating defense responses, stimulation of the PAG or the more rostral periventricular gray in humans has often been reported to be associated with feelings of anxiety or even “doom” or desire to escape.³⁷ Presumably other forebrain systems tap into the PAG-RVM system to fine-tune nociceptive processing. Evidence in support of this idea has been provided in imaging studies in humans showing activation of the PAG and decrease in pain rating in placebo conditions or when human subjects direct their attention away from a noxious stimulus.^{38,39}

Although the focus has long been on the ability of this brainstem modulatory system to diminish pain, it has been demonstrated that the PAG-RVM system can enhance sensitivity, producing hyperalgesia, or even potentially “spontaneous” pain.^{40,41} Evidence from behavioral studies in animals clearly demonstrates that the RVM is required for enhanced nociceptive responding in inflammatory and neuropathic models.⁴² Shifts in modulatory control reinforce the effects of primary and central sensitization discussed earlier. The facilitating RVM output is from a class of neurons called on-cells.⁴³ A link through pontine noradrenergic cell groups may also be involved. Recruitment of the PAG-RVM system to produce hyperalgesia is mediated at least in part by forebrain structures. For example, illness-induced hyperalgesia (i.e., the arthralgias and myalgias experienced by any of us with a flu-like illness) is known to be mediated by forebrain structures connected with the PAG-RVM system.^{44,45}

NEUROCHEMICAL REGULATION OF INTRINSIC MODULATORY SYSTEMS

It has been known for some time that the brainstem system described earlier utilizes endogenous opioids and is an important substrate for opioid analgesia. The PAG-RVM axis is rich in opioid peptides and opioid receptors, and direct local microinjection of μ -opioid agonists into either the PAG or RVM produces an analgesic effect that is as great as that produced by systemic administration of morphine. Morphine or μ -opioid agonists given systemically or applied focally within the RVM suppress the firing of on-cells and activate off-cells. The latter effect is indirect, through disinhibition. (See Heinricher and Morgan⁴⁶ for review.) μ -Opioid action at any one of these brainstem sites recruits the network as a whole, at least in part by inducing release of endogenous opioids at the other nodes. Thus, the effects of opioid microinjection in the PAG are mediated by endogenous opioid release within the RVM and at the level of the spinal cord. The opioid-mediated recruitment of the network as a whole following activation of one link is probably an important factor in the analgesic efficacy of this system.

One of the more interesting developments in understanding pain modulation has been the growing recognition that this opioid-sensitive system is regulated by a variety of neurotransmitters and neuropeptides. Among the neuropeptides that have been studied from this point of view are the endogenous kappa opioid agonist dynorphin, cholecystokinin (CCK), FMRFamide, and neurotensin. Each of these peptides can act as an "antiopioid," that is, interfering with the analgesic effects of a μ -opioid agonist without itself altering nociceptive responding.

Dynorphin and CCK are probably the best studied. Focal application of dynorphin within the RVM significantly attenuates the antinociceptive effect of PAG morphine, most likely by inhibiting the off-cells, which are normally activated by μ -opioid agonists. CCK applied at a low dose within the RVM attenuates the analgesic effect of systemically administered morphine by preventing opioid activation of the off-cells, the RVM inhibitory output neuron.⁴⁷ Endogenous CCK clearly opposes the analgesic actions of opioids because administration of CCK antagonists potentiates the analgesic effects of systemically administered morphine. There is evidence that the diminished opioid efficacy in some clinical pain states is due to up-regulation of CCK.⁴⁸ At higher doses, CCK applied within the RVM has an effect by itself, producing hyperalgesia. The actions of CCK within the RVM contribute to enhanced responding in an animal model of nerve injury pain.⁴⁹

Neurotensin has a similar dual role within the RVM. The observation that a neurotensin receptor antagonist potentiates the analgesic effects of morphine applied within the PAG demonstrates that endogenous

neurotensin opposes the analgesic actions of the opioid. Focal application of exogenous neurotensin within the RVM has a bidirectional effect on nociception: low doses produce hyperalgesia, whereas high doses produce analgesia.⁵⁰ The neural basis for this bidirectional action is a selective activation of RVM on-cells at the low neurotensin dose, with recruitment of off-cells when higher doses are given.⁵¹

CONCLUSION

As early as 1911, Head and Holmes⁵² suggested that sensory and affective components of pain sensation were mediated by distinct neural circuits. An elaboration of this concept, that pain sensation has several aspects processed through distinct neural channels, subsequently became widely accepted.⁵³ However, it is only recently that findings from animals and from imaging studies in humans have been combined to provide a firm experimental basis for the idea that information related to pain is detected by multiple molecular transducers on several classes of primary afferent neurons, conveyed over parallel pathways, and processed in a distributed cortical network. The complexity of this picture is further compounded by plasticity of nociceptive circuits and by modulatory systems that regulate communication of the afferent input. These new perspectives underscore the importance of linking the continuing advances from animal studies with clinical and experimental findings in humans.

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