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Pain and stress : Theoretical perspectives of interaction with the immune and endocrine systems*

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Pain Perception

Pain is a conscious and localized perception of discomfort or distress caused by the stimulation of specialized nerve endings called nociceptors. At one time, it was thought that there were no specific receptors for pain sensation, that is, overstimulation of various types of skin receptors would cause pain. However, Zotterman(1939) demonstrated the existence of nociceptors. Nociceptors are sensory receptors that respond to the stimulus when it reaches a certain level of intensity which will cause tissue damage. They originated from myelinated A–delta fibers and non myelinated C fibers in peripheral nerves. The diameters of A–delta and C fibers are less than 6 μ and 0.3 to 1.3 μ respectively. The conductance velocities are less than 36m/sec for A–delta fibers and 0.5 to 0.2m/sec for C fibers. Myelination and the diameter of axons are factors in conduction velocity. Thus, A–delta fibers carry fast pain and C fibers carry slow pain. These fibers have different thresholds for painful stimulation.

Pain has at least three different qualities: a bright, pricking sensation (fast pain), a burning sensation (slow pain) produced by C fibers, and lastly a visceral and deep somatic pain. Pain can be caused by the following four forms of sensory modalities: electrical, mechanical, chemical,and thermal. Since many nociceptors respond not only to a single modality, they are called polymodal nociceptors. This polymodal characteristic of nociceptors is perhaps the basis of the varicty of pain qualities in human pain perception.

The most investigated nociceptors are those of the skin. Zimmermann and Zotterman (1976) studied C–fiber thermal nociceptors in the skin of cats. They demonstrated that the total number of impulses per stimulus and the maximum frequency of the impulses both increase linearly with the skin temperature. Thus, it is suggested that the nociceptor not only responds to a noxious stimulus but also it carries infomation about stimulus intensity. From electrophysiological data (Head, Rivers & Sherren: 1905), heat pain threshold was found to be about 45℃ in man. Zimmermann and Zotterman (1976) also demonstrated that after a total block of conduction in myelinated and nonmyelinated fibers (produced by crushing), a redevelopment of C–heat fibers occurred and that these fibers had relatively lower thresholds by about 3.7℃ (the threshold is 45℃ in normal nerves). This neurophysiological feature of peripheral nerves is the basis of the hyperalgesia which is seen in the pathology of chronic pain.

Neurophysiological and Neuroanatomical Basis of Pain

There are two types of hyperalgesia:

1. Hyperalgesia derived from tissue damage and occurring in damaged tissue (primary hyperalgelgesia)
2. Hyperalgesia derived from tissue damage but occurring in normal tissue adjacent to the damaged tissue

These primary and secondary types of hyperalgesia give rise to a variety of clinical pain syndromes. For example, paradoxical pain caused by the hyperalgesia of the peripheral nervous system is characterized by stimuli which are ordinary not noxious but which are now perceived as painful. In this sense paradoxical

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pain is not imaginary pain.

According to Handwerker (1976), responses in nociceptive cutaneous heat receptors are modulated by endogenous agents produced in the process of inflammation. These are for example, bradykinin, prostaglandin E, histamine, serotonin, and substance P. The existence of these endogenous substances may provide a pharmacological model of hyperalgesia and chronic pain. These algesic substances may function to excite nociceptors, and since the production and decomposition of the algesic substances are slow, excitation of nociceptors lasts for a long time. If the concentration of the substances is not sufficient to excite the nociceptors,they can produce sensitization. The analgesic effect of acetylsalicylic acid (aspirin) is also explained along this line, as acetylsalicylic acid inhibits the synthesis of one of these substances, prostaglandin.

Information from nociceptors of the skin, viscera, and muscle enters the dorsal horn of the spinal cord via the A–delta and C fibers. Dorsal horn neurons ascend to the thalamus (ventral posterior lateral nuclei) via lateral spinothalamic tracts. There are, however, additional spinal asending pathways which carry nociceptive information. This is the reason why pain will return after a cordotomy. Pain transmission is also controlled by descending corticofugal influences coming from the cortex, the diencephalon,and the brainstem.

Inhibition of Pain (analgesia)

Reynolds (1969) reported that electrical stimulation of the periaqueductal gray matter in the unanesthetized rat resulted in the inhibition of pain. Carstens, Yokota, and Zimmermann (1979) examined spinal neuronal responses to noxious stimulation of the periaqueductal gray matter, and found that the discharge of a spinal neuron was inhibited to less than 1/3 of the control. Thus, the periaqueductal gray matter has a definite function in controlling the transmission of pain. Samanin and Valzelli (1971) demonstrated that stimulation of the dorsal raphe nuclei for one hour before the injection of morphine remarkably increased the analgesic effect of the drug. Thenen (1967) tested the interrelationship between pain and serotonin and found that low concentrations of serotonin lead rats to develop hyperalgesic behavior. Akil and Liebeskind (1975), studying the effect of norepinephrine, dopamine, and serotonin in analgesia, found that the diminishing effect of PAG stimulation over time can be restored by injection of 5–hydroxytryptophan or L–dopa, and that decreasing serotonin concentration reduced the analgesia, while increasing concentrations enhanced it. From these data it is indicated that neurotransmitters have an important role in pain-inhibitory mechnisms. It is also suggested by Mayer and Liebeskind (1974) that narcotic analgesia (morphine) and stimulation-produced analgesia are similar in action, and that a common mechanism may exist for both of them.

As previously mentioned in the case of hyperalgesia mediated by endogenous substances such as bradykinin, prostagrandin E, histamine, and substance P, it is very plausible to hypothesize the existance of endogenous substances which take part in the inhibition of pain. In fact, in 1975, Terenius (1975) and Hughes (1975) independently discovered endogenous substances which are like opiates in their action in the brain. Further, Akil,Mayer and Liebeskind (1976) demonstrated that naloxone, an opioid antagonist, reversed the analgesic effect produced by electrical stimulation.

Stress Analgesia and its Neurochemical and Neuroanatomical Mechanism

Interestingly, Akil, Madden, Patrick, and Barchas (1976) demonstrated that acute stress increased the level of opiate peptides and decreased pain in the rat and that this stress-induced analgesic effect was partially reversed by naloxone. Lewis, Cannon, and Liebeskind (1980) and Lewis, Sherman,and Liebeskind (1981) further examined the mechanisms of stress-induced analgesia and suggested that opioid and non-opioid mechanisms of stress analgesia exist.

Moreover, Levine, Gorden, and Fields (1979) demonstrated that placebo analgesia was reversed by naloxone in opiate-naive subjects, suggesting that placebo analgesia was also mediated by endorphin. Mayer, Price, Barber, and Rafii (1976) examined the relationship between acupuncture analgesia and naloxone and found that acupuncture analgesia is also mediated by endogenous opioids.

Stress and Susceptibility

In the context of stress analgesia, the relationship between stress and susceptibility to disease should be metioned. Davis and Read (1958) subjected mice to fighting stress. They, then inoculated them with Trichinella spiralis and found large numbers of Trichinella spiralis in the fighting rats as compared to those rats that were kept separate. Soave (1964) reported that crowding reactivated a rebies virus infection in a guinia pig 8 month after inoculation. Chang and Rasmussen (1964) demonstrated that polyoma virus infection of newborn mice increased the incidence of tumors when sound or avoidance learning stress was given.

However, Marsh et al. (1963) reported that exposure to a stressful avoidance situation (pressing a telegraph key at a steady rate to avoid a shock to the tail) resulted in a marked decrease in susceptibility to poliovirus infection in monkeys. This result contrasts with the previous findings which are basically characterized by stress-induced increase of susceptibility to infection. As Marsh et al. (1963) suggested, the schedule of exposure to stress may be an important factor for the fluctuation of susceptibility to infection. Thus, it is suggested that stress can increase susceptibility to infection in general although there are some exceptions, for example duration of stress, type of animal species, and infectious agent used.

This increase in susceptibility induced by stress is considered to be due to an immunosuppressive influence of the adrenal corticosteroids such as corticosterone. Giron et al. (1973) showed that some steroid hormones such estrone, cortisone, and hydrocortisone markedly enhanced experimental viral infections, whereas other steroids, prednisolone, progesterone, and testosterone had no effect. It has been suggested that interference with the interferon system is a possible mechanism by which viral infections are enhanced by hormones. Alteration of cell membranes and stimulation of viral replication are other possible mechanisms which may underlie the viral infection-enhancing activity of steroid hormones.

So far it has been discussed that some stress analgesia is based on a mechanism involving endogenous opioids and that stress-induced increace of susceptibility to infection or to disease is based on infection-enhancing activity (reducing resistance ageinst disease) of steroid homones. The secretion of steroid hormones from the cortex of the adrenal gland is mainly controlled by adrenocorticotrophic homone (ACTH).

Stress and Endocrine System —ACTH and Cortisol and their Secretion under Stress—

ACTH is a peptide with 39 amino acids (human) stored in the pituitary gland. ACTH-secreting cells of the adrenohypophysis, (anterior pituitary gland) require regular stimulation by corticotrophin release factor (CRF). The major site of CRF synthesis is located in the basal hypothalomus. Its secretion is mediated by neurotransmitter such as norepinephrine, acetylcholine, and serotonin. Thus, secretion of ACTH is under direct control between ACTH and cortisol. Negative feedback inhibition of ACTH secretion is exerted by cortisol, which also inhibits the secretion of CRF. The site of feedback effect of cortisol is not clear. However, three major possible sites have been considered; pituitary gland, hypothalamus, and mesencephalic and limbic system structures. In this sense, areas of the central nervous system outside of the hypothalamus also have an important role in ACTH regulation. For example, electrical stimulation of the amygdala facilitates ACTH release (Matheson et al., 1971). Mangili et al. (1966) suggested that the hypothalamus and septum have a reciprocal relationship with the amygdala to regulate ACTH secretion. It is known that electrical stimulation of these neuroanatomical sites decreases ACTH secretion induced by stress, while destruction of the sites enhance ACTH secretion. Uhlir et al. (1974) demonsurated that lesions of the medial and lateral septal nuclei resulted in a lowering of the threshold of stimulation necessary to induce a corticosterone response to stressful stimuli. It is also suggested that the septum has a modulatory effect on both the threshold and the magnitude of activation of the pituitary-adrenal axis.

The function of central neurotransmitters to control ACTH secretion is very difficult to evaluate. Van Loon (1974) reported that direct infusion of Epinephrine into the basal part of the hypothalamus resulted in release of ACTH from the pituitary.

However, a catecholamine antagonist such as reserpine or chlorpromazine also caused release of ACTH and cortisol in the rat and dog. This suggests that catecholamines have both excitatory and inhibitory roles in the regulation of ACTH secretion. Thus, a possible effect of catecholamines in the regulation of ACTH secretion is conflicting. Krieger (1977) reviewed recent studies on the effect of serotonin on hypothalamic-pituitary function and reported that serotonin has been inplicated in exercising both stimulation and inhibition of ACTH release. Elevated serotonin concentrations had no effect on the plasma corticosteroid response to stress. Decreased serotonin concentrations had either no effect or was associated with an increased or decreased response to stress. This suggests that the role of serotonin in the pituitary-adrenal response to stress is unclear.

Stress and Immune System

Selye (1952) stated three stages of general adaptation:

(1) the alarm reaction, in which adaptation has not yet been acquired

(2) the stage of resistanse, in which adaptation is optimum

(3) the stage of exhaustion, in which the acquired adaptation is lost again.

Stress causes the discharge of ACTH. Many investigations have proved that stress is the most important factor for the secretion of ACTH. Some of the diseases classified as general adaptation syndromes are now recognized as autoimmune diseases. This implies that there may be some possibility of an interaction between stress and the immune system, i.e., exposure to stress is followed by a decrease in host defene mechanisms.

Some major components of host defense mechanisms against microorganisms are granulocytes, macrocytes (macrophages), lymphocytes, and immunoglobulins (antibodies). The primitive lymphoid cells from the bone marrow differentiate into two lymphocites; T-lymphocytes and B-lymphocytes. T-lymphocytes are responsible for cell-mediated immunity and B-lymphocytes function as a synthesizer of circulating antibodies. Although T-lymphocytes do not themselves secrete antibodies, T-cells cooperate with B-lymphocytes in antibody synthesis. There is also interaction between macrophages and T and B cells.

Macris et al. (1970) demonstrated that lesions of the anterior hypothalamus in the guinea pig resulted in a suppression of the delayed cutaneous hypersensitivity response to picryl chloride and to tuberculin. Keller et al. (1980) reported that the lesions of the anterior hypothalamus in the guinea pig resulted in significantly smaller cutaneous tuberculin reactions than in the controls. However, the percentage and absolute number of T and B cells were not significantly changed after the hypothalamic lesions. This suggests that the inhibition of lymphocyte stimulation in blood by anterior hypothalamic lesions does not appear to be related to a decrease of T lymphocytes.

Tyrey et al. (1972) demonstrated that the anterior hypothalamic lesions resulted in a depression of the antibody titer. This depression was prevented when hypophysectomy was carried out at the same time that the hypothalamic lesions were produced. This finding supports the concept that the antibody titer depression may result from an increase in ACTH release from the pituitary after the production of the hypothalamic lesions. In human experiments, Greene, et al. (1978) found a statistically significant negative correlation between social stress and cellular immunity, that is, when stress increased, lymphocyte cytotoxicity decreased. Palmblad, et al. (1976) demonstrated that the interferon-producing ability of the blood increased in absolute values during and after 77-hour sleep deprivation and that phagocytosis by peripheral blood phagocytes showed a decrease during the sleep deprivation and was followed by a rise to levels above pre-exposure values. Monjan and Collector (1977) investigated short term exposure of aminals to sound stressors and showed that this clearly depressed the lymphocyte-mediated cytotoxic response. Longer exposure caused an enhancement of cytotoxicity of lymphocytes. It is plausible to hypothesize that the stress-induced suppression of immunologic competence is mediated by the endocrine system, especially through cortisone. However, the mechanism for the immunological hyperactivity (enhancement of Cytotoxicity of lymphocytes) is not yet fully understood.

Neurotransmitter and Immune System

The interaction between the central nervous system and the immune system also has been investigated in connection with neurotransmitters. Idova and Devoino (1972) demonstrated that administration of serotonin and its precursor 5–hydroxtryptophan into immunized mice lengthened the latent period of synthesis of antibodies. Lowering serotonin levels in the brain have the opposite effect upon production of antibodies. Eremina and Devoino (1973) showed that lesions of the midbrain raphe nucleus (serotonin containing neurons) resulted in significant changes both in the dynamics and in the intensity of the primary immune response in the rabbit. Antibody formation in animals with lesions of the midbain raphe nucleus markedly increased in the initial period of the productive phase of the immune response. It is suggested that the hypothalamohypophseal system takes part in this inhibitory effect of brain serotonin upon production of humoral antibodies.

The role of the dopaminergic system upon the immune system is not clearly understood. However, Cotzias and Tang (1977) demonstrated that high propensity for breast cancer in mice was associated with low dopamin-stimulated adenylate cyclase activity in the brain. The function of the adrenergic system upon the immune system is also vague and experimental data are contradictory. However, Besedovsky et al. (1979) found diminished NA content in the spleen during the immune response. Kasahara et al. (1977) investigated the effect of sympathectomy with 6–hydroxydopamine on antibody formation to sheep red blood cells, and found that chemical sympathectomy suppressed the primary immune response. These data provide some evidence for existence of a relationship between the sympathetic nervous system and the immune system and for an immunosuppressive effect of NA.

Engel et al. (1977) reported the binding of α-bungarotoxin to epithelial cells of thymus, indicating the presence of nicotinic acetylcholine reseptor on these cells. Besides, Bourme et al. (1974) suggested that cyclic AMP may inhibit amplification of an immune response, whereas cyclic GMP was shown to reverse this inhibitory effect. It is also suggested that symathetic neurohormones (catecholamines) may act on the immune response through cyclic AMP, and that the parasympathetic neurotransmitter, acetylcholine, may act through cyclic GMP. Thus,there seems to be a push-pull mechanism between cyclic AMP and cyclic GMP to regulate functions of lymphocytes.

Stress Analgesia and Immune System

A possible functional interaction between stress analgesia and the immune system is an interesting topic for further investigation. Althouth there is little experimental data available to predict such an interaction between stress analgesia and immunological response, Wybran et al. (1979) investigated the influence of morphine, dextromoramide, levomoramide, and methionine-enkephalin upon human T blood lymphocytes. They found that mornhine and dextromoramide inhibited the percentage of active T rosettes. On the other hand, Methionine-enkephalin increased this percentage. These effects were reversed by naloxone. It is suggested by the author that human blood T lymhocytes may have surface receptor-like structures for morphine, dextromoramide, and methionine-enkephalin. Bourne et al. (1974) also reported that decreases of cyclic AMP levels or cyclic AMP/cyclic GMP ratios activate inflammatory reactions. This suggests that cyclic AMP may have an important effect in modulating inflammation and immunity responses.

Although time courses for pharmacological and neuroendocrinological mechanisms of stress analgesia and immunity are quite different and therefore it is difficult to introduce a satisfactory hypothesis for a possible interaction between stress analgesia and immunity, further investigations about cellular mechanisms of cyclic AMP and cyclic GMP in modulation of inflammation and immunity responses will hopefully further our understanding of the neuropharmacological mechanism of stress analgesia.

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要　約

痛みの抑制（無痛覚；analgesia）は Reynolds (1969) の導管周辺部の電気刺激実験や Samanin and Valzelli (1971) の縫線核の電気刺激実験によって，そのメカニズムの神経解剖学的および薬理学的な背景が明らかにされつつある。また，Akil ら (1976) が急性ストレスがラットの体内の阿片様ペプタイドを増加させ，痛みを減少させ，その効果がナロキソンで逆転しうることを発見してから，痛みとストレスの関連がストレスにより引き起こされる無痛覚（stress analgesia）として注目されてきている。

本論文では，痛みの生理学的および解剖学的基礎を痛覚の伝導経路，痛覚を伝える神経線維の種類，痛みの主要3種（早い痛み，遅い痛み，内臓痛および身体深部の痛み）などについてレビューし，痛みや炎症を起こす物質，ヒスタミン（histamine），ブラディキニン（bradykinin）プロスタグランディンス　Eタイプ（Prosta-

glandins E）セロトニン（serotonin），P物質（substance P）と痛覚過敏（Hyperalgesia）との薬理学的メカニズムが示された。さらに痛覚の抑制とストレスによる無痛覚の現象が神経化学的および神経解剖的側面から論じられ，ストレスによる無痛覚と内因性オピオイド（生体内で分泌される阿片様物質）の関連性が述べられた。

次にストレスと感受性（罹患性）が内分泌系のACTHおよびコーチゾールの分泌及びそれらの免疫抑制作用の側面から述べられ，ステロイドホルモンに感染への感受性を高める（病気にかかりやすくなる）作用のあることが指摘された。

そしてストレスと免疫系の関係が胸腺リンパ球と抗体の合成機能を有する骨髄リンパ球について Tyrey ら（1972）の実験にみられるような前部視床下部の破壊が抗体価を減少されるという観点から論じられた。また，神経伝達物質と免疫糸の関係がAMP（アデノシン一燐酸）とGMP（グアノシン一燐酸）の働きの側面から検討され，カテコールアミンはサイクリックAMPを，そしてアセチルコリンはサイクリックGMPをそれぞれ媒介として免疫系の反応に影響をおよぼす可能性が示唆された。

ストレスによる無痛覚と免疫系の相互作用は現在のところ強力な実験知見が得られていないが非常に興味深い課題である。ストレスによる無痛覚と免疫系は薬理学的にも，また神経分泌学的にもメカニズムやその時継列上の特徴が異なるが，炎症や免疫性反応に関するサイクリックAMPとサイクリックGMPの細胞レベルのメカニズムを追求することにより，ストレスによる無痛覚の神経薬理学的なメカニズムがより深められると考えられる。