Pain

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Abstract

Since the pain is an obscure expression of mental suffering induced by several factors and individual emotional susceptibility, should be analized the character and variation of the pain from onset of present suffering according to systematic detection before to do anything of medical or surgical treatment. In this review, the nature of receptors or algesic agents to evoke the pain and the mechanism of conductive relationship of afferent impulses between paleo and neo spinothalamic tracts under pathophysiological and cytochemical standpoint, then theoretical mechanism of analgesia will be discussed for the successful management of pain.

「痛み」は，複数の因子および個体の情緒感受性とによって引き起こされている漠然たる苦悩の表現であるから，いかなる内科的または外科的治療を行うに当たっても，まず現症について発症時からの痛みの性質や変動を系統的な手段に従って分析すべきである。本文ではまず病態生理学的ならびに細胞生理学的な立場から見た「痛み」を惹き起こす受容体および発痛物質の本質について，次に相対峙する脊髄網様系および脊髄視床系における求心性インパルス伝導の相互的役割について述べ，最後に（これらを踏まえた）正しい疼痛管理を目指した理論的な鎮痛機序について現在までの論文を引用して述べる。

Key words

nociperceptor, chemoreceptor, opioid-receptor, algesic chemical agent, anticonvulsant

I. Introduction:

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, characteristically serves as a warning sign of onset of disorder or a reflecrt of pathologic condition in the pain conduction system except normal process in childbirth.

Since the character of pain frequentry fluctuates with time progress and emotional susceptibility, a careful analysis of the nature of pain and point out the real feature or rule out the confused signs by detective work, often lead to find out the hidden disorder related to the present suffering. How the pain began, arised location and the mode of radiation, all of them imply important clues of the disorder.

It is generally presumed that pain is a sensory, realized on cerebral cortex by projected final impulses which were transmitted through the legal channel or the collateral path way of somatic and autonomic nervous systems when evoked on

the pain receptors existing at distal parts of the body or on any part of the pain conduction system.

The receptors for pain has been naturally thought as nociceptive throughout the process of injury or any other disorder, however, the character of pain develops into variously with time progress, it suggests that another affective factor (s) may be accumulated on or close to the receptors in the following process of injury or disorder, then it influences on the receptors as chemoreceptive.

While the pain evoked by any nociception or injury are readily blocked by morphine and other narcotic analgetics, but not by non-narcotic antipyretic analgetics such as aspirin. The above evidences lead to point out that aspirin affects on neither the central nervous system nor the nociperceptors, and morphine may be affects on both or either of them, because mental disturbance never happen by aspirin but it usually occurs by morphine, moreover selective analgesia is possible by intrathecal administration of morphine but quite impossible by aspirin in the same method.

Another interesting evidence is an effect of anticonvulsants for the relief of the pain of the trigeminal nerve tic douloureux. In spite of nothig efficacy for another nature of pain, why diphenylhydatoin or carbamazepine has excellent analgetic effect against only trigeminal and glossopharyngeal neuralgia. It has been customarily used without clear mechanism, however the anatomical relationship between trigeminal nerve and crossed artery in the posterior fossa strongly suggested the mechanism of the onset of tic douloureux then, related mechanism of anticonvulsants for the relief of the pain of tic douloureux has become agreeable.

Current managemant of pain thus, theoretical analysis for the pain should be done before any application to be attempted.

II. The Nature of the Pain Receptors and Algesic Chemical Agents

Although the morphological structure of the pain receptor is unknown, there are, currently, two opposing concepts of receptor: (i) pain is a specific modality like vision or hearing "with its own central and peripheral apparatus", and (ii) pain is produced by intense stimulation of nonspecific receptors since "there are no specific fibers and no specific endings". The latter concept is derived from the work of Sherrington[1], who drew attention to the apparent lack of specificity of the nerve endings or receptors for pain. However, the physiological display of pain is quite suggestive of coexistence of specific endings or receptors close to the nociperceptor, because each evidence has individual feature and character of pain and variously fluctuates progressively.

The concept that some chemical products influences on uninjured nerve endings to evoke various of pain was speculated and confirmed by Lim[2], who demonstrated artificial pain evoked by either natural or synthetic bradykinin repeatedly without apparent injury to the receptors.

Other chemical agents, among them amines (histamine, 5-HT or serotonin, acetylcholine) and polypeptides (arginyl-bradykinin, lysyl-bradykinin, methionyl-lysyl-bradykinin, substance P, angiotensin, arginyl-vasopressin, lysyl-vasopressin) and prostaglandin (PGE, PGI) have been found to be highly active in producing pain by intra-arterial or intra-peritoneal application.[3][4] Certain chemical agents elevates the susceptibility of nerve fibers or endings specifically, it seems as peculiar receptors for pain has been demonstrated on the nerve endings or close to it and chemical products are a reliable component to evoke the pain.[5]

It does not rule out the classical causal relationship between nociception and pain, but indicates that receptor or axon may be stimulated accidentally and unspecifically as they lie in the path of injury.[6]

Accordingly, there is provided with the possibility to evoke an inexplicable pain at anywhere through the axon even nothing of injury or disorder at visible distal part as certain cranial nerve neuralgia.[7]

From these considerations it might be easily explained that the initial momental sensation of

injury, thermal burn and any other attack is realized likely one of impact frequently lack of pain, however promptly fall into various sensation with pain in proportion to the grade of attack.

Current opinion regarding to the receptor for pain is supported by the above evidences that the intact receptor responses naturally as nociceptive if adequate stimulus has given, but essentially as chemoceptive.

On the site of injury, the peripheral circulation slows down as the result of injury itself or due to the liberation of vasoactive agents such as histamine and serotonin lead to the accumulation of blood corpuscles, then bradykinin and other peptides which favorable to evokes pain are composed from the broken fragments of accumulated corpuscles or released from the lysosomes of leucocytes and other cells.[8] They are postulated to cause further vasodilatation with increased vascular permeability and finally constitute inflammation.[9] The paravascular sensory nerves to end in unmyelinated free branching terminals in connective tissue spaces close to the capillaries and venulles[10] everywhere throughout the body, thus appear to be the chemoreceptors for pain. Since bradykinin is readily destroyed by kininase in plasma or lymph, if circulation does not improve the pain cannot be far removed from the capillary area.

In early stage of malignant neoplasm usually not indicates pain or any other unpleasant sensations, also even in advanced stage until tissue damage or involved nerve system has become destructive. With the progress of destruction the beneficial relief for the pain are limited to narcotic analgetics or nerve block, and non-narcotic antipyretic analgetics quite ineffective, because they act as to block the synthesis of certain algesic chemicals which affects on the chemoreceptors, so that cannot block the pain after proximal part of receptors has been involved.

The above evidences conclusively suggests that the normal uninjured pain receptor is naturally nociceptive but essentially chemoceptive.

III. The Mechanism of Pain

Pain is a final response of cerebral cortex for afferent impulses which were transmitted through the spinothalamic tract and the paleospinothalamic tract both which arise from dorsal horn in the spinal column as well known as second neurons.[11]

The spinothalamic tract are composed by neospinothalamic fibers and connected with third neurons at thalamus, and the paleospinothalamic tract are composed by numerous spinoreticular fibers, so that probably connected with final neurons at reticular formation and hypothalamus or limbic system of archicortex. The relationship or the conductive order between the spinothalamic tract and the paleospinothalamic tract is not yet well understood, however it to be thought that the spinothalamic tract always influences on the paleospinothalamic tract dominantly, then emotional reaction and actual existence of pain may be realized on the cerebral cortex.[12]

Nerve fibers have been classified into three groups according to their size as A, B and C. Large A fibers is further classified into α, β, γ, and δ in proportion to their size. Among of them, A-δ is myelinated fiber and approximately 3~6 μ in diameter hold 15~40 m/second of conduction velocity, and smallest C is unmyelinated fiber and approximately 0.5~1 μ in diameter hold 0.5~2.5 m/second of conduction velocity.[13]

Hardy, Wolff and Goodell (in 1952) speculated as different character of pain which (i) momental, sharp and localized impact may be transmitted by large A-delta fibers named quick pain and (ii) continuous, violent would rather unlimited suffering follow to quick pain may be transmitted by small C-fibers so called slow pain, probably cooperate through same afferent path individually with time lag then may finally be realized as an complexed pain on the cerebral cortex.[14][15] Since a part of sympathetic afferent path which composed by C-fibers and arised from nucleus intermediolateralis of spinal column links with same and more upper or lower level of paraver-

tebral sympathetic trunks through gray communicans ramus, though under spinal anesthesia, bilateral sympathetic collateral path from peripheral area via sympathetic ganglions and trunks until not anesthetized level of them where communicated to the dorsal horn of spinal column through white ramus are still intact, therefore reasonably certain unpleasant sensation such as vascular pain may be realized.[16)17)]

In 1965, a new theory of pain mechanism has been reported by Melzack & Wall.[18)] It is one of the self control system for pain held on substantia gelatinosa (SG) and first central transmission cells (T) of dorsal horn based on the difference of conduction velocity between large and small afferent fibers affects on both SG and T as cooperatively, then the impulses to restrictively be controlled together with negative feedback impulses toward central transmission system like as gate control. The above of "gate control theory" is still evaluated as a basic concept of pain mechanism.

As an electrophysiological study, quite interesting evidence has been reported by Reynolds [19)] that highly effect of analgesia was observed in rat by electro focal stimulation of brain, and simialr evidence were demonstrated in cat[20)] and man[21)] in 1977. Bowsher[22)] speculated about those phenomenons that the opioid receptors located on the cytochemical circuit in the substantia gelationosa of dorsal horn may be occupied by released endorphins through efferent impulses of electro stimulus, then the opioid receptors play a part of postsynaptic or presynaptic inhibition for the nociceptive input neurons.

Endorphins means endogenous substances

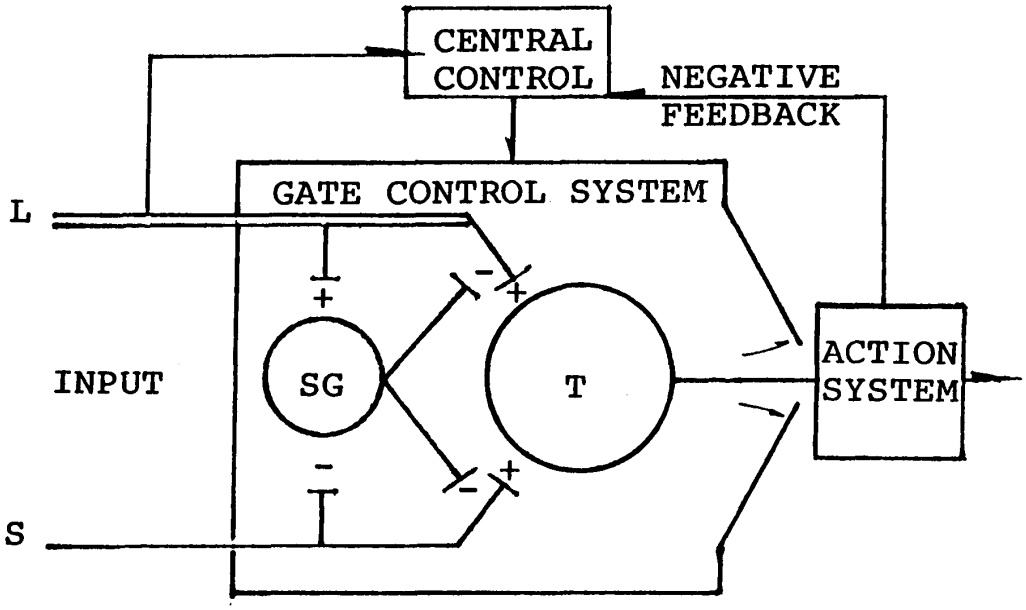

Fig. 1. Schematic diagram of the gate control theory of pain mechanism. L: the large-diameter fibers, S: the small-diameter fibers. The fibers project to the substatia gelationosa (SG) and first central transmission (T) cells. The inhibitory effect exerted by SG on the afferent fiber terminals is increased by activity in L fibers and decreased by activity in S fibers. The T cells project to the entry cells of the action system. The central control trigger is represented by a line running from the large-fiber system to the central control mechanisms, in turn, project back to the gate control system together negative feedback impulses to the central transmission system.
+ : Excitation, − : Inhibition.
(modified illustration from original of Melzack R. & Wall P. D. 1965)[18)]

within morphine, it is one of a family of opioid-like polypeptides originally isolated two pentapeptides by Hughes and Kosterlitz in 1975 from the brain of animal.[23]

Little before, researchers had concluded that the complex interactions among morphine-like drugs, antagonists, and mixed agonist-antagonists could best be explained by postulating the existence of more than one type of receptor for the opioids and related drugs.[24]

Endogenous opioid peptides recently, three distinct families have been identified as: the enkephalins, the endorphins, and the dynorphins. Each family is derived from a genetically distinct precursor polypeptide and has a characteristic anatomical distribution. These precursors are now commonly designated as proenkephalin, pro-opiomelanocortin, and prodynorphin. However the detailed mechanism of releasing or inhibitory process of endorphins for the relief of the pain are not well known, probably the reflected efferent impulses play a role of trigger if the afferent input potency beyond the threshold and pain has maintained, because quantitative endorphins in the cerebrospinalfluid has shown increasing tendency in parallel of intensity and duration of pain, and no doubtful clinical evaluation of endorphins for the relief of the pain has been established when apllied into spinal subarachnoidal space.[25]

Pain thus, has not been realized by only afferent component, but certainly placed under arranged situation by own synchronized controll mechanism.

Ⅳ. The Mechanism of Analgesia

A. Non-Narcotic Analgetics

Non-Narcotic antipyretic analgetics have been established favourable situation for the relief of the pain.

Since analgetic doses of these derivatives do not cause mental disturbances, hypnosis, or changes in modalities of sensation other than pain, their action had been speculated as play on a subcortical site.

The speculation was clearly demonstrated by Lim[2] in 1967 with (1) Cross-perfused splenic method and (2) Central and peripheral cannula method. The demonstration was observed under cooperating in conscious two dogs how the analgesic effect of aspirin display against evoked pain by bradykinin on the vaso-isolated but innervated spleen of a recipient dog R connected by cross perfusion with a donner dog D. Two remarkable evidences were observed that: (a) evoked pain in dog R by bradykinin injection into the splenic artery of dog R is blocked when aspirin or any other non-narcotic antipyretic analgetics is injected into the blood of dog D perfusing the spleen of dog R, but block does not occur when the analgetics injected into the brain circulation via the brachiocephalic artery of dog R. (b) the opposite is true that with the narcotic analgetics blocked bradykinin-evoked pain only when given to dog R intravenously.

The above results indicates a block site of aspirin is not central but peripheral, and narcotics is quite opposite. Speculatively to be thought that morphine and other narcotic analgetics probably block synaptic transmission in the central pathways for pain, and aspirin and other non-narcotic antipyretic analgetics acts peripherally by blocking the generation of impulses at the chemoreceptors for pain.

In 1970, Vane[26] and his colleagues discovered a fundamental evidences that aspirin and aspirin-like drugs has an inhibitory effect for an enzyme which synthesizes prostaglandins from the unsaturated fatty acid and arachidonic acid as a physiological precursor of some prostaglandins.

Since prostaglandins are found in inflammatory exsudates and produce an inflammatory response on intradermal injection, aspirin and aspirin-like derivatives play a part of blocking the generation of some chemical substance like prostaglandin. Certainly, prostaglandin E_1 (PGE_1) has pain producing effect, however the principal action of PGE_1 is not to produce overt pain but to sensitize the chemoreceptors.[27]

The experimental evidences of Lim and his comment therefore, might be modified more clearly

as an analgetic effect of aspirin for induced pain by bradykinin play principally on the process of systhesis of some chemical products which to sensitize the chemoreceptor as PGE_1, because bradykinin is never eliminated by aspirin, but readily destroyed by kininase in plasma, and aspirin never inhibits the susceptibility of nociperceptor in an effective dose for the relief of the pain.

B. Narcotic Analgetics

Recent studies of narcotic analgetics has been concentrated on the opioid receptors located on the substantia gelatinosa of the dorsal horn.

The concept of opioid receptors was intr-oduced by some interesting evidences that while morphine and morphinomimetic substances do not depress proprioceptive pathways in the dorsal horn, they produce an unusually intense, prolonged and segmental analgesia when injected into the spinal subarachnoidal or epidural space of animals and human.[28]

Possible mechanism or morphological structure of some receptors binding with narcotic analgetics in the spinal cord were investigated by immunohistochemical studies and autoradiographic studies.[29][30][31]

Surprisingly, there abundant opiate receptors existed in the substantia gelatinosa of the dorsal horn especially in Rexed's (1952) laminae 1 and 2, and more important that the spinal distribution of the enkephalin terminals were concentrated in

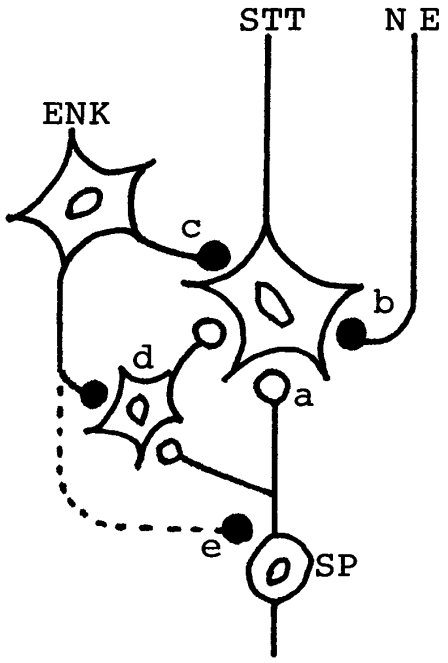

Fig. 2. Schematic cytochemical circuitry of the dorsal horn. Excitatory and inhibitory connections are represented by open circles and filled circles respectively. Excitatory afferent input (a) is illustrated as originating from an SP-containing primary afferent fiber. Descending input (b) is bulbospinal axon that inhibits the spinothalamic tract (STT) postsynaptically by norepinephrine (NE). The enkephalinergic interneuron (ENK) inhibits the STT postsynaptically (c). The SP excitatory and ENK inhibitory controls may be exerted through another excitatory interneuron (d) of the dorsal horn. The broken line is a possible enkephalinergic presynaptic control of the primary afferent fiber (e). (modified illustration from original of Basbaum A. I.: Advances in pain research and therapy,1985)[32]

substantia gelatinosa,[32)33)] where the selective pharmacological depressing effects of narcotics has shown on nociceptive pathways by epidural or intrathecal administration.

The enkephalins are synthesized on a single precursor molecule, proenkephaline A, which produces six copies of methionine-enkephalin and one of leucine-enkephalin. Although some enkephalin immunoreactive bulbospinal axons project to the spinal cord, the vast majority of spinal enkephalin derives from intrinsic neurons of the dorsal horn.[34)]

Enkephalin terminals are concentrated in laminae 1 and 2, and relatively dense in lamina 5, in lamina 7 and just lateral to the central canal.

In early studies, two major modes of action of the spinal dorsal horn enkephalin neurous have been proposed.

(1) The distribution of the opiate binding sites has demonstrated as high concentrations associated with primary afferents.[35)] Other studies reported a loss of opiate receptor binding in rats which treated neonatally with capsaicin.[36)] Since capsaicin selectively destroys relatively small diameter of primary afferent axons, these data provided indirect evidence that the opiate binding site is located on unmyelinated, C, and possibly A-δ afferents. Furthermore, since capsaicin also renders analgesia in rat, it is likely that afferent nociceptors are opiate-receptor-laden, some of which contain substance P (SP).[37)] More important, these studies directed attention to a possible presynaptic control of opioid peptide for primary afferent nociceptors.[38)]

Jessel and Iversen,[39)] demonstrated that opiate and opioid peptides blocks the potassium-evoked release of SP from slices of trigeminal nucleus, i. e., the medullary dorsal horn. Later, Mudge et al.[40)] reported that enkephalins blocks the calcium spike and concomitantly release of SP from cultured dorsal root ganglion cells.

Taken together, these studies suggested that the release of the putative neurotransmitter SP from small-diameter, possibly nociceptive afferents, could be presynaptically controlled by opiate interactions with opiate receptors located on the primary afferents.

(2) A postsynaptic hypothesis is supported by following anatomical and physiological studies. First, some spinothalamic tract neurons of laminae 1 and 5 (some of which are likely to be nociceptive) are directly contacted by (i. e., are postsynaptic to) enkephalin terminals.[41)] Some of these neurons probaly recieve a convergent enkephalin and SP input.[42)] Later, electrophysiological studies have been demonstrated that dorsal horn neurons were hyperpolarized by enkephalin via an increased potassium conductance.[43)] In figure 2, some of circuits through which enkephalin neurons may control the out put neuron, both direct and indirect postsynaptic inhibitory controls are illustrated.

The third hypothesis is that other opioid peptides located in the dorsal horn provides the presynaptic input to the opiate receptor. With the discovery of the dynorphin family of opioid peptides and the report of profound analgetic effects of intrathecal administration of dynorphin, the possible relationship of spinal dynorphin systems to anti-nociceptive mechanisms has been presumed in the spinal column.[44)]

Basbaum et al.[45)] demonstrated several striking differences in the anatomical distributions of immunoreactive enkephalin and dynorphin that the dynorphin staining pattern was consistent with it having a particularly significant contribution to nociceptive mechanisms. In contrast to the dense enkephalin terminal distribution in laminae 1 and 2, there is extremely limited dynorphin terminal staining, moreover, it is restricted to the region of lamina 5, and only a few scattered fibers were located in the outer part of substantia gelatinosa. In neither the TNC (trigeminal nucleus ganglion) nor the spinal dorsal horn was there terminal staining in the inner part of the substantia gelatinosa, where enkephalin terminals are most heavily concentrated. The analysis of the sacral cord suggested a much denser terminal staining pattern than observed in the TNC, rather than deriving from local interneurons, so that it might be concluded that most of the dynorphin terminals

in the sacral cord originate in primary afferent fibers. These proposal was based on the remakable similarity of the dynorphin staining in the sacral cord to that revealed with antisera directed against vasoactive intestinal polypeptide, [46)47)] a peptide that clearly originates in primary afferents, and to the spinal cord terminal arborization of pelvic visceral afferents demonstrated by the transganglionic transport of horseradish peroxidase.[48)]

Splendid analgetic effects in clinical application of a small amount of morphine or other synthesized morphinomimetic substances for subarachnoidal or extradural space[49)] is supported the above evidences and the proposed mechanism which speculated by Bowsher previously.

Terminology: The term "opiate" was once used to designate drugs derived from opium-morphine, codeine, and the many semisynthetic congeners of morphine. Soon after the development of totally synthetic entities with morphine-like actions, the word "opioid" was introduced to refer in a generic sense to all drugs, natural and synthetic, with morphine-like action. More recently, opioid has also been used to refer to antagonists of morphine-like drugs as well as to receptors or binding sites that combine with such agents.[50)]

C. Anticonvulsants

Anticonvulsants has been naturally used for the relief of or the prevention against the epileptoid seizure and expectantly applied for the relief of the pain of tic douloureux by Blom[51)] who treated with carbamazepine and reported them in 1963.

The effectiveness of carbamazepine in trigeminal neuralgia has been attributed to a diphenylhydantoin-like effect on synaptic transmission in the spinal trigeminal nucleus, but an effect not presents in the comparison agents phenobarbital as well known as one of the anticonvulsant.

Therefore, detailed mechanism of carbamazepine for the relief of the pain of tic douloureux is still uncertain, however it may certainly be suppresses spasm like transfer on subcortical site, because tic douloureux is quite resemble to epileptoid seizure in the arising mode.

The focus of trigeminal neuralgia has been also discussed for over the years, since intractable pain is often ceased temporarily by nerve block even detective focus or anything else of abnormalities cannot find out within corresponding area.[52)] The above evidences suggested that the anticonvulsant mainly inhibits either presynaptic or postsynaptic potentiation, or elevates excitatory synaptic threshold, and nerve block suppresses original afferent impuls which sensitizes focus or may be magnified at focus.

The etiological concept of tic douloureux has been reported in 1976 by Jannetta[53)] through of his work of surgical success, but essential machanism of anticonvulsants for the relief of the pain has not been clarified.

His work is based on a number of microsurgical decompression applied to the trigeminal nerve stem where compressed by pulsation of the small cranial artery in the posterior fossa. Currently, the microsurgical approach to the intracranial nerve is worth for a diagnostic determination of the focus of inexplicable cranial nerve disturbance and for permanent cure of intractable suffering such as tic douloureux, glossopharyngeal neuralgia including Bell's spasm those which any other proper managemant has not been established without side effects.

D. Other Miscellaneous

Ketamine belongs to the cyclohexylamine so called dissociative anesthetics because, when so used intravenously or intramuscularly, during induction, fall into dissociated feeling from environment including my own extremities of the recipient, ultimately amnesia with conspicuous analgesia has happen.

The mechanism of those evidences to be thought that one of the form of transmission or

communication disturbance of afferent impulses held on certain level of cerebral cortex, because a common categorical disagreeable dreams occasionally occur in spite of nothig else of remembers throughout the amnestic period.

E. Inhalational General Anesthetics

The state of general anesthesia is a drug-induced absence of perception of all sensations. While the intravenous agents, e. g. the barbiturates also induces similar state except analgetic effect, the nitrous oxide shows an analgetic stage before fall into amnesia. This is a principal reason of the inhalational sedation applied during dental procedure. In out-patient practice, the inhalational sedation is not only sedative aim, but also it is of greate practically use in the field of analgesia, because from 30 to 50 % of nitrous oxide with oxygen well maintain both of helpful analgetic effect and suitable consciousness.

The mechanism of inhalational analgetics including diethylether and halothane is also still uncertain. We attempted to make clear the mechanism of general anesthesia in the field of biochemical phamacology under a speculation that one of the transmission disturbance of subcortical site. Certain inhibitory effects of enzymatic activity which induced mambrane potential of excitable cell were observed in vitro.[54] However, it does not exceed experimantal state and our concept has not been accepted for all general anesthetics.

V. General Considerations for Management of Pain

Barbiturates is one of the intravenous anesthtics, seems an analgetic agent but frequently no helpful for excessive surgical procedure, since barbiturates is a hypnotic or sedative agent and has no analgetic effects. Aspirin quite no effective for the glossopharyngeal neuralgia, since glossopharyngeal disturbances belong to the identical category of the tic douloureux. So that, these ineffectiveness are attributed to the incorrect selection of agents for attempted procedure or the diagnostic failure. Narcotics has an excellent effect for the relief of the pain at any stage in any category of disorder, however, quite insufficient for complete elimination of the pain during surgical procedure in same dose of the postoperative analgesia, why? It might be attributed to the component of the afferent impulses which either has been modified at the nociception by own control mechanism or not yet been arrainged on the afferent path way by enkephalinergic interneuron pre or/and postsynaptically.

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