CHAPTER 2

LITERATURE REVIEW

Piper sarmentosum Roxb. (Piperaceae)

Piper sarmentosum Roxb., Family Piperaceae, which Thai local name is "Cha Plu" (Figure 1). Trease and Evan (1983) described that piperaceae consists of 4 genera and 2,000 species. This plant is tropical, biennial and mostly climbing shrubs or lianas with spikes and swollen nodes. The flower is bar shape that one-celled ovary has a single ovule and develops to a berry. The seeds contain abundant endosperm and perisperm.

Piper sarmentosum Roxb. consists of 2 strains as a climbing or creeping plant and widely distributed throughout Thailand. Other Thai name besides Cha Plu (Central part) are Plu-Ling (Northern part), Plu-Nok (East-Northern part) and Nom-Wa (Southern part). It is a terrestrial herb, 60 centimeter high, green trunk and jointed at the nodes. The leave was thin, 7-15 centimeter long, 5-10 centimeter wide, dark green color, heart shape and spicy taste. The leaves of *Piper sarmentosum* were used as vegetable or food wrapping (Saralamp, 1996; Suvatti, 1978).

Piper sarmentosum Roxb., contains many phytochemicals such as phenylpropanoids (ascaricin, α-ascarone) (Masuda *et al.*, 1991); xanthophylls, tannins, total phenolic compounds (Chanwitheesuk *et al.*, 2004); calcium, iron , vitamin B 1, 2, C, E, β-carotene (Subramaniam and Mohd, 2003) and β-sitosterol (Nimsa and Chantrapromma, 1983). The oxalic acid content is high which could combine with calcium in intestine to cause complex formation and block food absorption, and made calculus in bladder (Valyasevi and Dhanamitta, 1974).

Figure 1. *Piper samentosum* **Roxb. leaves**

According to the traditional medicine, this plant was used as expectorant, carminative, refreshing throat, flatulent and asthma relieved, enhancing appetite (Apisariyakul and Anantasarn, 1984), muscle pain relieving property (Ridtitid *et al.*, 1998), anti-amoebiasis (Rahman *et al.*, 1999), treatment of diabetes mellitus (Peungvicha *et al.*,1998) and flu relieved. Perry (1981) reviewed for their ethnomedical properties and reported that it is used to reduce fever in influenza and aids in digestion. The root is prepared for remedy for toothache fungoid dermatitis on the feet. In Malay Peninsula, leave was applied to the forehead of children with headache. A decoction of the boiled leaves might be utilized as an embrocation and rub to cure weakness and pain in the bones, and discoloration of skin. In Indonesia, the rootlets chewed with betel nut and the juice swallowed was beneficial for cough and asthma, chewed with ginger to treat toothache and chewed with nutmeg and ginger to treat pleurisy. At the same time, warm leave coated with coconut oil are applied to the painful chest and rheumatic patients (Pongboonrod, 1976; Muhammad and Mustafa, 1994).

Chemical constituents

Niamsa and Chantrapromma (1983) studied the chemical constituents of petroleum ether leaves extract of *Piper sarmentosum*. Two of them were identified as hydrocinnamic acid and β-sitosterol.

Likhitwittayawuid and colleagues (1987) reported six components isolated from the fruit of *Piper sarmentosum*. Two of them were β-sitosterol and the known unsaturated amide. The other four components consisted of the aromatic alkene, the pyrole amide and two unsaturated pyrolidine amides, which were named as sarmentine and sarmentosine.

Masuda and colleagues (1991) identified the benzene soluble fraction of the methanolic leave extract of phenylpropranoids. They are 1-allyl-2,4,5-trimethoxybenzene

is asarone, 1-(1-E-propenyl)-2,4,5-trimethoxybenzene is α-asarone. The compound, 1-allyl-2-methoxy-4,5-methylenedioxybenzene is asaricin and 1-allyl-2,6-dimethoxy-3,4-methylenedioxybenzene is a new natural product.

Strunz and Finlay (1995) synthesized sarmentosine that isolated from fruit of *Piper sarmentosum*. It was synthesized by a short efficient pathway in which the essential steps was an aldol-Grob fragmentation sequence, and the overall yields was 21%.

Aunpak and colleagues (1997) examined chemical compositions of essential oil distilled from the leaves and fruits of *Piper sarmentosum* and revealed that longifolene (24.30%), β-caryophyllene (10.11%), allo-aromadendrene (13.51%) and 9-epi-(E)-caryophyllene (18.24%) were the major constituents of the leaf oil whereas β-caryophyllene (31.11%), β-asaron (26.65%), viriflorene (9.28%) and β-selinene (8.21%) were the major constituents of the fruit oil.

Chanwitheesuk and colleagues (2004) studied the antioxidant of methanol leaves extract of *Piper sarmentosum* that contained vitamin C, vitamin E, carotenes, xanthophylls, tannins and total phenolic compounds.

Rukachaisirikul and colleagues (2004) extracted *Piper sarmentosum* fruits with hexane and methanol. The study found guineensine, brachystamide B, brachyamide B, 1-piperettyl pyrrolidine, 3′,4′,5′-trimethoxycinnamoyl pyrrolidine, α-asarinin, sesamin and methyl piperate (Figure 2).
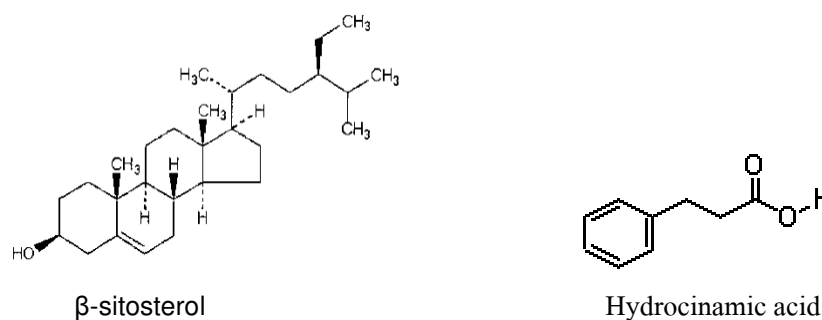

β-sitosterol   Hydrocinamic acid

Figure 2. The molecular structures of various compounds found in *Piper sarmentosum*

Sarmentine

Sarmentosine

α-asarone

β-asarone

Trimethoxybenzene

β-selinene

α-asarinin

Sesamin

1-piperettyl pyrrolidine

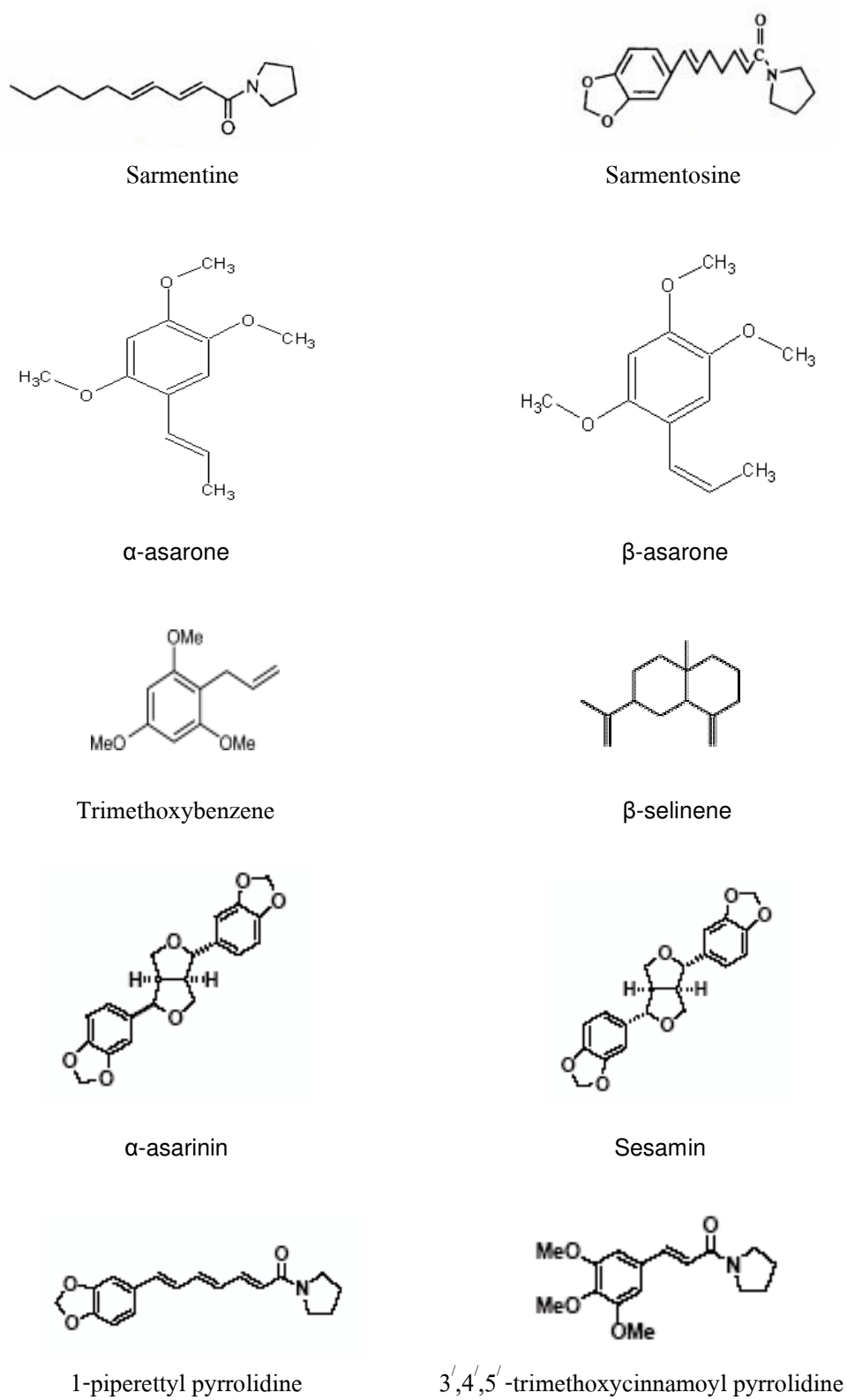$3',4',5'$-trimethoxycinnamoyl pyrrolidine

Figure 2. The molecular structures of various compound found in *Piper sarmentosum* (continued)

Pharmacological activities

Pongmarutai (1980) reported that the crude aqueous extract of *Piper sarmentosum* leaves reduced blood glucose in alloxan-induced diabetic rabbits, however, it had no effect in normal fasted rabbit. The administration of the extract to maturity-onset diabetic patients resulted in a reduction of blood glucose level. The methanolic extract from *Piper sarmentosum* leaves, however, could not reduce blood glucose in normal rabbits.

Apisariyakul and Anantasarn (1984) studied on the pharmacological activity of eleven Thai medicinal plants to screen for their cathartics and antispasmodics activities. It has been found that *Piper sarmentosum* was able to decrease the intestinal tension and also inhibit the acetylcholine-induced intestinal tension in isolated rat ileums.

Sunbhanich and colleagues (1988) reported the pharmacological effects of the crude methanol extract of *Piper sarmentosum* on the isolated guinea pig ileum and the isolated rat phrenic nerve hemidiaphragm preparation. The results showed that the extract could produce an increase in both frequency and amplitude of contraction of ileum while atropine could only slightly antagonize the effect. In rat phrenic nerve-hemidiaphragm preparation, the extract produced a slightly twitch potentiation followed by depression. They concluded that the extract acted like a cholinergic agonist on the ileum and a depolarizing neuromuscular blocking agent on the neuromuscular junction.

Masuda and colleagues (1991) reported that the benzene soluble fraction of the methanolic leave of *Piper sarmentosum* extract showed antimicrobial activity against *Escherichia coli* and *Bacillus subtilis*.

Aunpak and colleagues (1997) reported that the essential oils, distilled from the leaves and fruits of *Piper sarmentosum*, inhibited the growth of *Pseudomonas aeruginosa*, *Bacillus subtilis* and *Candida albicans*.

Peungvicha and colleagues (1998) studied on the hypoglycemic effect of the water extract of whole plant of *Piper sarmentosum* by examining in normal and streptozotocin-induced diabetic rats. The results showed that a single oral administration of the water extract at the dose of 0.125 and 0.25 g/kg significantly lowered the plasma glucose level in normal rats. The repeated oral administration of the water extract at the dose of 0.125 g/kg for 7 days produced a significantly hypoglycemic effect in the diabetic rats.

Ridtitid and colleagues (1998) reported that crude methanol extract of *Piper sarmentosum* possessed a marked neuromuscular blocking activity in rat phrenic nerve-hemidiaphragm preparation. This is possibly due to an inhibition on the acetylcholine release at the pre-synaptic terminal.

Rahman and colleagues (1999) showed that when chloroform and methanolic extract of *Piper sarmentosum*, *Andrographis paniculata* and *Tinosora crispa* were tested for antimalarial effect against *Plasmodium falciparum* and *Plasmodium berghei* parasites *in vitro* and *in vivo*, the results showed that the chloroform extracts were more active than the methanolic extracts *in vitro*. Although the extract of *Piper sarmentosum* was effective, the activity of *Andrographis paniculata* demonstrated higher antimalarial activity than other two plants *in vivo.*

Sawangjaroen and colleagues (2004) reported the studies of crude methanolic extract of *Piper longum* fruit, *Piper sarmentosum* root and *Quercus infectoria* nut gall against *Entamoeba histolytica* infected in caecum of mice. The results showed *Piper sarmentosum* was effective as an antiprotozoal agent.

From the pharmacodynamic point of view, the analgesic, anti-inflammatory and antipyretic properties of compounds of methanol extract of *Piper sarmentosum* leaves have not been investigated. Therefore, the purposes of the present study were verify for the analgesic, anti-inflammatory and antipyretic activities and investigate possible mechanisms produced by the methanolic extract of *Piper sarmentosum* leaves in comparison with standard drugs as aspirin and morphine.

Pain

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage (Balestrieri and Fisher, 1994). It is a personal and subjective experience, protective mechanism for the body. It occurs whenever any tissues are being damaged and causes the individual to react reflexly to remove the pain stimulus called withdrawal reflexes (Guyton, 1997). The emotional or psychologic state of the patient may result in pain in the absence of tissue damage or other pathology and may modify the character of the pain.

The pain experience is divided into 2 types as acute or chronic pain. Both of these experiences alter the comfort level of the patient and cause different pain reaction behaviors.

Acute pain is a warning to possible or real danger. The onset of this pain is sudden and a temporary duration. The behavioral response is based on the activation of the sympathetic nervous system with release of epinephrine-norepinephrine. Acute pain is usually accompanied by physiological and behavioral response. Examples of physiological responses are increase in heart rate, respiration, blood pressure, peripheral blood flow, muscle tension, sweating, dilated pupils and behavioral responses include distress, restlessness and inability to concentrate.

Chronic pain is persist beyond the normal healing time as pain signals are repeatedly being generated marking neural pathways hypersensitive to pain signals and resistant to antinociceptive input. There are no physiological responses in chronic pain. But the behavioral response is based on the long-term activation of the autonomic nervous system. The patient can exhibit sleep and appetite disturbances, irritability, decreased libido, loss of interests and increased preoccupation with body sensations. The patient can also experience apathy, withdrawal, hopelessness and depression (Beyers, 1991).

Quality of pain has been classified into 2 different major causes as fast pain and slow pain.

Fast pain is also described by many alternate names such as sharp pain, pricking pain, electric pain and acute pain. This type of pain is felt when a needle is stuck into the skin or when the skin is cut with a knife. This pain is also felt when the skin is subjected to electric shock. The fast pain is transmitted through type Aδ pain fibers.

Slow pain is also described as burning pain, aching pain, throbbing pain, nauseous pain and chronic pain. This type of pain is usually associated with tissue destruction. It can become excruciating and lead to prolonged, unbearable suffering. It can occur both in the skin and in almost any deep tissue or organ. The slow pain results from stimulation of the more primitive type C fibers (Moffett and Moffett, 1993; Guyton, 1992).

Pain mechanisms

Neurophysiology of pain

Noxious or nociceptive stimuli activate highly developed endings on primary afferent (sensory) neurons, this term called pain receptors or nociceptors (Richard, 1995). They are widespread in the superficial layers of the skin and internal tissues as arterial walls, the joint surface. Transduction of these stimuli gives rise to action potentials that are transmitted along the afferent neuron into the dorsal horn of the spinal cord. A-delta (Aδ) fibers are small myelinated conducting afferent neurons, 2-5 μm in diameters which conduct rates of 12-30 m/s, rapidly that terminate in lamina I and V of the spinal cord. They have a relatively high threshold for activation by mechanical and thermal stimuli and mediate sharp, prick and localized pain, often termed somatic pain. C fibers are larger unmyelinated afferent neurons, 0.4-1.2 μm in diameters which conduct rates of 0.5-2 m/s, slower conducting. They are polymodal, and are activated by mechanical, thermal or chemical stimuli. They terminate in larmina I and II of the spinal cord (substantia gelatinosa) (Ganong, 2001:a) and mediate dull, diffuse, aching or burning pain, sometimes called visceral pain. Aδ and C fibers release excitatory amino acids in dorsal horn (glutamate), C fibers also release neuropeptides (substance P) (Stephen, 1998) (Figure 3).

Peripheral sensitization

After tissue damage which may be caused by mechanical, chemical or thermal (below 15 ºC, above 45 ºC) on nociceptor, biological molecules are produced such as substance P, histamine, hydrogen ions, bradykinin, prostaglandin, nitric oxide, ATP. Bradykinin is a main substance that stimulates nociceptors (act on Bradykinin 2, BK_2 receptor) via protein kinase C (PKC), and prostaglandin (mainly E_2, I_2), sensitize nociceptors (act on EP/IP receptor) to noxious stimuli by lowering of nociceptor activation thresholds via cyclic-adnosine monophosphate (cAMP). Its causes the afferent neuron to discharge, sending impulse (action potential) to the

spinal cord. This state is called peripheral sensitization (Guyton, 1992; Mutscheler and Derendorf, 1995:b) (Figure 4).
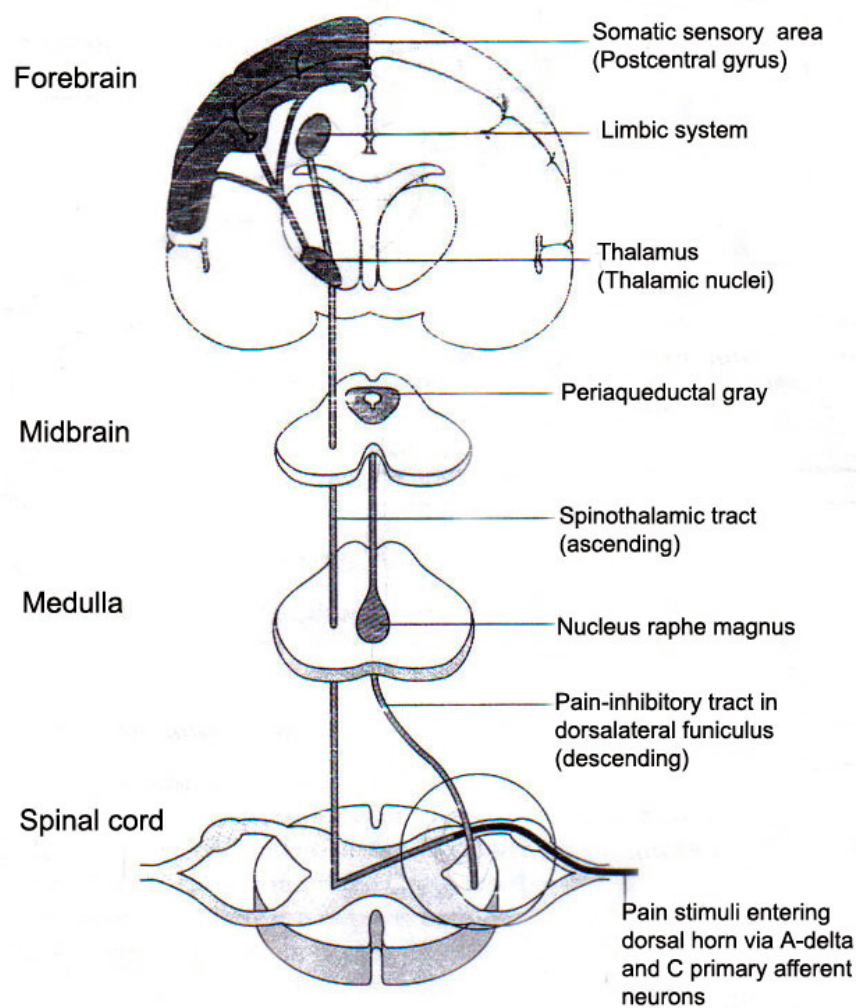
Forebrain — Somatic sensory area (Postcentral gyrus)

— Limbic system

— Thalamus (Thalamic nuclei)

Midbrain — Periaqueductal gray

— Spinothalamic tract (ascending)

Medulla — Nucleus raphe magnus

— Pain-inhibitory tract in dorsalateral funiculus (descending)

Spinal cord

Pain stimuli entering dorsal horn via A-delta and C primary afferent neurons

Figure 3. Pain pathway (Stephen, 1998)

Central sensitization

The repeated afferent impulse to the spinal cord as a result of the sensitizing biological molecules at the site of tissue damage, cause the dorsal horn neurons within the spinal cord to become hyperexcitable (William, 1998). When A-delta fibers produce the acute sensation of sharp and bright pain, their neurotransmitter in the dorsal horn is glutamate acting on Alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors. The C fibers can respond to a broad range of painful stimuli, including mechanical, thermal or metabolic factors. The pain produced is slow, burning, and long lasting. The neurotransmitter in the dorsal horn is glutamate along with certain peptides such as substance P (act on neurokinin 1, NK_1 receptor). The receptors for glutamate are not only AMPA, but also N-methyl-D-aspartate (NMDA). When AMPA receptor was activated and open following prolonged depolarization, continue stimulation of C fibers eventually causes greater excitation in the postsynaptic neurons in the dorsal horn as the NMDA receptors start added to the response. Recall that these only open with prolonged depolarization, such as would occur with prolonged pain. The resulting influx of Ca^{2+} cause trigger other long lasting cellular changes, so signal transduction coming to sensory projection fields in the cortex (postcentral gyrus). This part of the cortex, together with the thalamus, is responsible for the conscious perception of pain and particularly localizing and registering the intensity of the pain. The ascending reticular activating system has an influence on evaluation. The limbic system is responsible for emotional reactions triggered by pain while autonomic reactions are controlled by the hypothalamus (Mutscheler and Derendorf, 1995:b; William, 2000) (Figure 5). This state of hyperexcitability is called central sensitization. The whole concept of spinal cord nerve cells undergoing repeated stimulation and activation has been termed 'wind up' (Mill and Sayer, 1999).
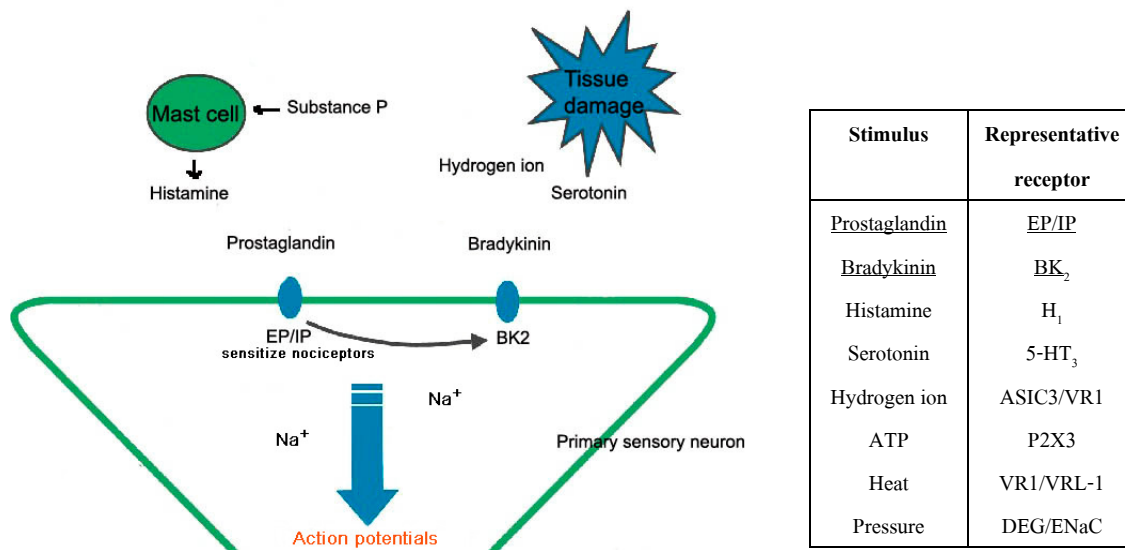
Figure 4. Pain pathway in peripheral sensitization (Adapted from Samad, 2002)

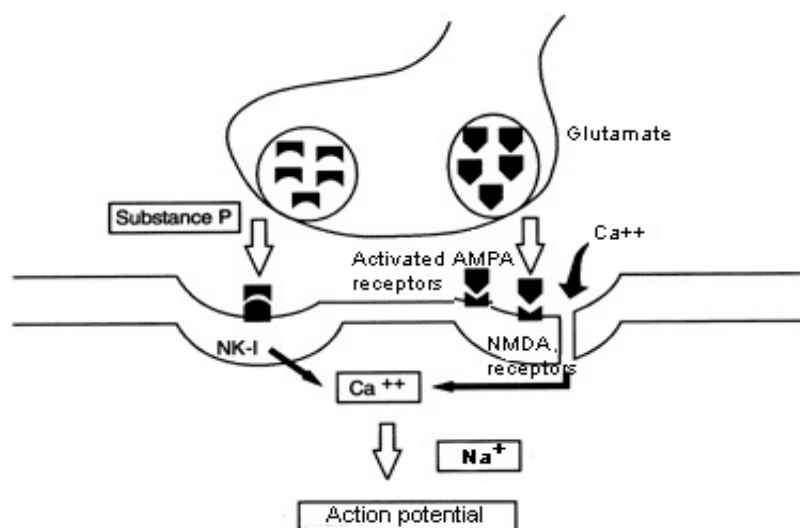| Stimulus	Representative receptor
Prostaglandin	EP/IP
Bradykinin	BK_2
Histamine	H_1
Serotonin	$5-HT_3$
Hydrogen ion	ASIC3/VR1
ATP	P2X3
Heat	VR1/VRL-1
Pressure	DEG/ENaC

Figure 5. Pain pathway in central sensitization (DeVane, 2001)

When biological molecules were spreading locally, causes areas near to the site of tissue damage to become involved, the nerve fibers become more sensitive, their pain threshold is lowered and spontaneous firing of afferent impulses occurs. The total effect on the patient is an increase in pain and greater sensitivity to a light touch that would normally not be painful called "allodynia" (Guyton, 1997).

The degree to which each person reacts to pain varies tremendously. This result partly from the capability of the brain itself to control the degree of input of pain signals to the nervous system by activation of a pain control systems called an analgesia system (Guyton, 1971). The analgesia system has major pathway sending the signal from thalamus and transmitted down in the spinal cord to a pain inhibitory complex located on µ and δ opiate receptors in the dorsal horn of spinal cord by transmitter substance, especially serotonin, norepinephrine and enkephalin. This point the analgesia signals can block the pain signals from peripheral nerves before it is relayed on the brain (Stephen, 1998).

Several subtypes of opiate receptor are known, and major subtypes are called Mu (µ), Kappa (κ) and Delta (δ) receptor. Each major opioid receptor has unique anatomical distribution in brain, spinal and the periphery (Gutstein and Akil, 2001). It is thought that µ receptors are responsible for supraspinal analgesia, respiratory depression, euphoria and dependency. These receptors have been further sub-typed as μ_1 which are supraspinal and mediate analgesia, and μ_2 which mediate respiratory depression. Enkephalins and endorphins are endogenous ligands for these receptors and morphine is an exogenous ligand. The μ_1 receptor is morphine selective. The µ-receptor is seen throughout the brain and spinal cord, with the highest concentration in amygdala, nucleus accumbens, thalamus, superior and inferior colliculi and nucleus tracts solitarus. Stimulation of κ receptors is thought to produce spinal analgesia, miosis and sedation. These receptors have been further subtyped as κ_1 which mediates spinal analgesia, κ_2 whose function is unknown. The κ_3 mediates supraspinal analgesia. Dynorphines are endogenous ligands at these receptors and morphine functions as an exogenous ligand. The κ receptors have been demonstrated in the brain and spinal cord, with concentration in preoptic area, hypothalamus and nucleus tracts solitarus. Stimulation of δ-receptors causes dysphoria, hallucinations, stimulation of vasomotor center, spinal and supraspinal analgesia. These receptors have been subtyped as δ_1, δ_2 and are thought to be relatively unimportant in terms of analgesia. Enkephalins are the endogenous ligands and morphine is exogenous ligand. The δ receptors are widespread

throughout the primary telencephalon (Mutschler and Derendorf, 1995:b). In animal models, the μ, κ and δ opioid receptors mediate supraspinal and spinal analgesia (Gutstein and Akil, 2001) (Table 1). The μ, κ and δ opioid agonist-antagonists are such as morphine-naloxone, etorphine-diprenorphine and DPDPE- naltrindole, respectively (Table 2)

Table 1. Classification of opioid receptor subtypes and action from animal models
     (Gutstein and Akil, 2001)

	RECEPTOR SUBTYPE	ACTONS	
		AGONISTS	ANTAGONISTS
Analgesia :			
Supraspinal	μ, κ, δ	Analgesic	No effect
Spinal	μ, κ, δ	Analgesic	No effect
Respiratory function	μ	Decrease	No effect
GI tract	μ, κ	Decrease transit	No effect
Psychotomimesis	.κ	Increase	No effect
Feeding	μ, κ, δ	Increase feeding	Decrease feeding
Sedation	μ, κ	Increase	No effect

All the correlation in this table are based on studies in rats and mice, which occasionally show species difference. Thus, any extensions of these associations to human begins are tentative.

Table 2. Actions and selectivities of some opioids at the various opioid receptor classes

(Gutstein and Akil, 2001)

Agent	Receptor types		
	μ	κ	δ
Drugs			
Morphine	+++	+	
Methadone	+++		
Etorphine	+++	+++	+++
Levorphanol	+++		
Sulfentanil	+++	+	+
Bremazocine	+++	+++	++
U50, 488		+++	
U69, 593		+++	
DPDPE			++
DSLET	+		++
Naloxone	---	--	-
Naltrexone	---	---	-
CTOP	---		
Diprenorphine	---	---	--
Naltrindole	-	-	---
Endogenous Peptides			
Met-enkephalin	++		+++
Beta-Endorphin	+++		+++
Dynorphin A	++	+++	
Dynorphin B	+	+++	+

+ = agonist, - = antagonist

Regulation of Body Temperature

The regulation of body temperature in human is a biological control system that has evolved to maintain thermal homeostasis. The control of body temperature within narrow limits is dependent upon the coordinated activities of several subsystems of the body (Seeley *et al.*, 1996). The physiological control system that coordinates the responses for effective regulation of body temperature is a negative feedback system with at least three major components such as vasomotor response, metabolism, sweating response and shivering (Wenger, 1995). The effector organ systems that determine heat production or heat loss and an integrator or controller that compares the sensed temperature to a "normal" or "reference" temperature to determine whether it is high or low. It activates the appropriate effector systems, which return the body temperature back to normal (Figure 6).

The balance that maintains a constant total body heat content can be expressed by the relation as follow.

Heat output = Heat input + Heat production

Heat input ⟶   [Heat production from metabolism]   ⟶ Heat output
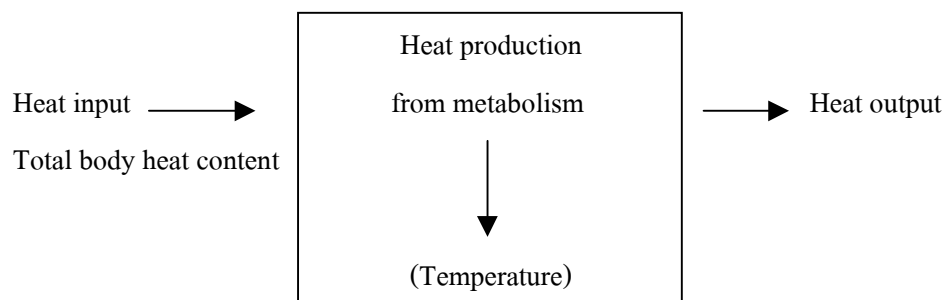Total body heat content

(Temperature)

Figure 6. Balance of heat input, output and production (Seeley *et al*., 1996)

Temperature receptors are divided into 2 pathways.

1) **Peripheral thermoreceptor in temperature regulation**

Temperature receptors that measure skin temperature are located beneath the skin. Peripheral temperature receptors are naked nerve ending that are very sensitive to temperature and classified as cold receptors or warm receptors (Rhoades and Pflanzen, 1992). Cold receptors are characterized by increasing steady-state discharge rates as the skin is cooled (10-38 ºC) and

afferents for cold are Aδ and C fibers. In contrast, warm receptors are those which steady state discharge rates increase in response to warming of the skin (30-45 ºC) and afferents for warm are C fibers, but above 45 ºC or below 15 ºC causes tissue damage begin and the sensation becomes one of pain (Julius, 2001). Nerve impulses from peripheral receptors enter the spinal cord at all levels and ascend to the brain.

2) Central Thermoreceptors in Temperature Regulation

Central thermoreceptors are found in deep body areas including the hypothalamas, spinal cord, abdominal viscera and great veins. Central thermoreceptors include both cold receptors and warm receptors that are uniquely sensitive to decrease or increase in body core temperature. Nerve impulses from core receptors feed into the brain, where they are integrated with thermal information from peripheral nerves (Julius, 2001).

So, sensors that detect changes in body temperature are located in both peripheral areas and in the central nervous system. However, the important sensory activity and the integration of the various feedback loops involved in the maintenance of a constant body temperature that take place in the preoptic hypothalamus (Ernest, 1993).

When the body temperature changes to the higher or lower set-point, new balance of heat loss and heat production is achieved in other responses that called "adaptation". Below a skin temperature of 20 ºC and above 40 ºC, there is no adaptation, but between 20 ºC and 40 ºC there is adaptation. In the 43-50 ºC, capsaicin receptors mediate warmth response (Ganong, 2001:a).

Response to heat

1. Sweating : Secretion of sweat to reduce body temperature is the function of the two to three million eccrine sweat glands located over body surface. Under extreme heat stress, they can produce sweat at a rate as high as 2 liters per hour.

2. Vasodilatation and cardiac output : The evaporation of sweat provides only local cooling, and it is the peripheral blood flow that determines how much heat can be carried from the core to be dissipated on the body surface. An early response to heat exposure is therefore described peripheral (skin) resistance to blood flow. This vasodilation permits increased peripheral blood flow, especially as cardiac output also being to rise (Jame, 1992).

Response to cold

1. Shivering : The muscular or myogenic response to cold in humans is the shivering reflex. It is a noncoordinated activity of skeletal muscle, it can interfere with normal motor movement and it may actually increase heat loss by convection because it agitates the surrounding medium.

2. Nonmyogenic heat production : In response to cold the body can also reflexly increase heat production in nonmuscular tissue by adipose tissue. This is triggered by catecholamine secretion, but this response is less important in humans (Lamb *et al.*, 1980).

3. Vasoconstriction : The major reflex response to cold in human is peripheral vasoconstriction. When the skin temperature is low, the heat conductance of fully vasoconstricted skin approximates 0.12 Cal/m^2/1ºC/min similar to that of cork. This is caused by stimulation of the posterior hypothalamic sympathetic center (Jame, 1992).

Many disease states cause fever, which is a regulated increase in body temperature beyond the normal range. Therefore, measurement of a person's body temperature is a common way to assess the illness. Some pathophysiological conditions produce either hypothermia or hyperthermia, which are unregulated decrease or increase, respectively, in body temperature.

Fever and Hyperthermia

The goal of thermoregulation is to maintain the core body temperature at an average nearly constant temperature to 98.6 ºF (37 ºC). The primary centers for processing of thermal information are located in the anterior hypothalamus. The incoming impulses from thermoreceptors in the skin and inner temperature sensors are integrated and translated into regulatory signals when a temperature adjustment is needed (Julius, 2001). When there is too much heat such as in physical exercise, blood flow to the skin and perspiration increase. In case of cold stress, peripheral vasoconstriction decreases dissipation of heat and heat production is also increased (Seeley *et al*., 2000).

Fever is an elevation of body temperature due to a "resetting of the thermostat" in the hypothalamas. A person with a fever still regulates body temperature in response to heat or cold. The most common cause of fever is infection, physical trauma and stress.

The onset of fever during infection is frequently gradual but it is most striking when it occurs rapidly in the form of a chill. The brain thermostat is suddenly raised the person feels cold and marked vasoconstriction and shivering occur (Seeley *et al.*, 2000). The person also curls up and puts on more blankets. This combination of decreased heat loss and increased heat production serves to drive body temperature up to the new set point where it stabilizes. It will continue to be regulated at this new value until the thermostat is reset to normal and the fever break (Jame, 1992). The person then feels hot throws off the covers and manifests profound vasodilation and sweating.

Fever caused by all infections, components of pathogenic microorganisms, including endotoxins of gram-negative bacteria and viruses. The components involved in this process are called exogenous pyrogens. They stimulate phagocytes to release endogenous pyrogens (EP) that probably circulate in blood to act on the thermoreceptors in the hypothalamus or perhaps, other brain areas, altering the rate of firing and their input to the centers. In other cases, EP may be produced by macrophage-like cells in the liver and stimulate neural receptors that give rise to afferent neural input to the hypothalamic thermoreceptors (Wenger, 1995; Vander, 2001).

The term EP was coined at a time when the identity of the chemical messenger was not known. At least one peptide, interleukin 1 (IL1) is now known to function as an EP, but other peptides such as interleukin 6 (IL-6) play a role too (Wenger, 1995). In addition to their effects on temperature, IL-1 and the other peptides have many other effects that have the common denominator of enhancing resistance to infection and promoting the healing of damaged tissue. All peptides belong to the large family of chemical messengers called cytokines.

Interleukin-1 causes the formation of prostaglandin (PG), mainly PGE_2, which alter metabolism of thermoregulatory cells in the hypothalamus via cAMP second messenger-mediated mechanisms (Guyton and Hall, 2000:a). The result is an increase in set point for thermoregulation to a higher temperature. When body temperature is elevated above the set point, it called "hyperthermia". So, inhibitors of cyclooxygenase as aspirin, block the fever response by inhibiting IL-1 stimulated PGE_2 synthesis in the hypothalamus by a direct action at the hypothalamus. (James and Steven, 1995) (Figure 7).

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                    ┌─────────────────────────┐
                    │    Exogenous pyrogen     │
                    └─────────────────────────┘
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                       │    Phagocytes     │
                       └──────────────────┘
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                       ┌──────────────────┐
                       │  Interleukin-1,6  │
                       └──────────────────┘
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        │   Thermoregulatory center in hypothalamus        │
        │                     │                            │
        │                     ▼                            │
        │           Prostaglandins (PGE₂)                  │
        │                     │                            │
        │                     ▼                            │
        │                   cAMP                           │
        ├────────────────────────────────────────────────┤
        │  heat production ↑          heat release ↓       │
        │                     │                            │
        └─────────────────────┼──────────────────────────┘
                              ▼
                       ┌──────────────┐
                       │    Fever      │
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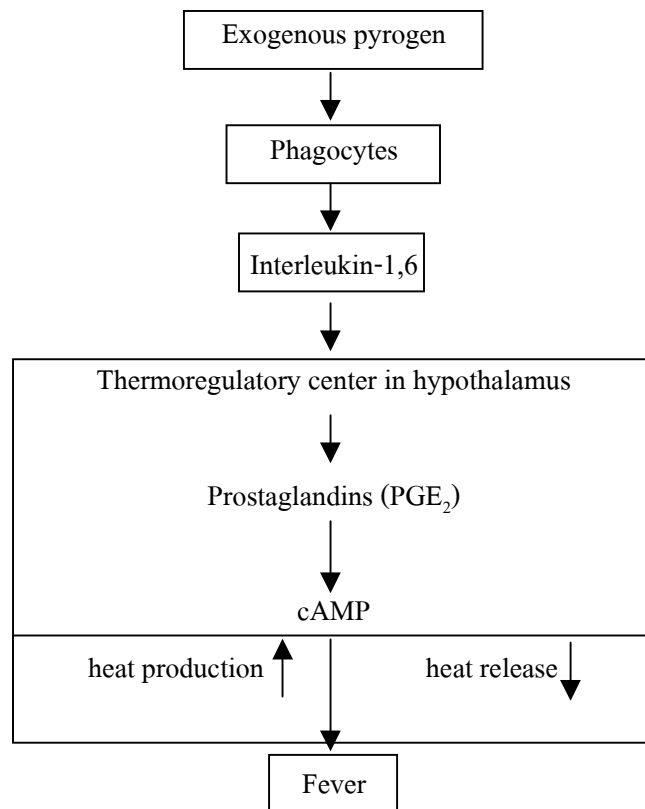
Figure 7. Reaction chain that resets the thermoregulatory center and results in fever

(Mutschler and Derendorf, 1995:b)

Immediately after readjustment of the target level, the normal body temperature of 98.6 ºF (37 ºC) is perceived as too cold. The response is cutaneous vasoconstriction, shivering and a subjective feeling of cold. The fever subsides with readjustment to the normal set point in the thermoregulatory center. Then, the increased temperature is perceived as too warm which results in sweating, vasodilation of skin vessels and subjective feeling of heat (Jame, 1992).

Fever implies hyperthermia, but not all cases of hyperthermia constitute fever. This important distinction is predicated on the fact that the heat producing or conserving mechanisms in fever are promoting an increased body temperature whereas during exercise-induced hyperthermia, for instance, the cooling mechanisms are shriving to return the body temperature to its normal steady-state. This is illustrated in Table 3, which compares data from two hyperthermia individuals. Both are now resting at a normal neutral environment of 31 ºC. This is cooler than the neutral temperature for the fever patient, so this person reflexly produces

heat by shivering. This reduces heat loss by vasoconstriction and the sweat response is also stopped. In the other person with exercise-induced hyperthermia, heat loss is increased through evaporation and vasodilation, and extra heat production is minimized. Only when the fever "breaks" does the patient begin to sweat in order to restore the body temperature to normal (Ernest, 1993).

Table 3. Thermal response during fever and physiologic hyperthermia (Ernest, 1993)

Variable	Exercise hyperthermia	Fever
1) Body temperature		
- Actual	39	39
- Steady-state	37	39
2) Environmental temperature		
- Actual	31	31
- Neutral	31	33
3) Response		
- Sweating	+	0
- Vasoconstriction	0	+
- Reflex heat production	0	+

The two individuals were resting at 31ºC. All temperatures are given in degrees Celsius,

+ = increased, 0 = no response.

Inflammation

Inflammation is defined as the reaction of a tissue and its microcirculation to a pathogenic insult. It is characterized by the generation of inflammatory mediators and movement of fluid and leukocytes from the blood into extravascular tissues (Fantone and Ward, 1999) or when tissue injury occurs, whether caused by bacteria, trauma, chemicals, heat or other phenomenal, multiple substance that causes dramatic secondary changes in the tissue are released by the injured tissues (Mariab, 2001). This is frequently an expression of the host's attempt to localize and eliminate metabolically altered cells, foreign particles, microorganisms or antigens. Inflammation has been divided into 2 phases, acute inflammation and chronic inflammation.

I. Acute Inflammation

The inflammatory responses consist of changes in blood flow, increased permeability of blood vessels and escape of cells from the blood into the tissues. Acute inflammation is short-lasting, in a few days. If it is longer lasting, it is progress to chronic inflammation. Various examples of acute inflammation are sore throat, reactions in the skin to a scratch or a burn or insect bite, and acute hepatitis (Stanier and Forsling, 1990).

Causes of Acute Inflammation

1. **Microbial infections** : One of the common causes of inflammation is microbial infection. Viruses lead to death of individual cells by intracellular multiplication. Bacteria release specific exotoxins, which specifically initiate inflammation, or endotoxins, which are associated with their cell walls. In addition, some organisms cause immunologically-mediated inflammation through hypersensitivity reactions. Parasitic infections and tuberculous inflammation are instances where hypersensitivity is important.

2. **Hypersensitivity reactions** : A hypersensitivity reaction occurs when an altered state of immunological responsiveness causes an inappropriate or excessive immune reaction which damages the tissues. The types of reaction have cellular or chemical mediators similar to those involved in inflammation.

3. **Physical agents** : Tissue damage leading to inflammation may occur through physical trauma, ultraviolet or other ionizing radiation, burns or excessive cooling or frostbite.

4. Irritant and corrosive chemicals : Corrosive chemicals such as acids, alkalis, and oxidizing agents, provoke inflammation through gross tissue damage. However, infecting agents may release specific chemical irritants which lead directly to inflammation.

5. Tissue necrosis : Death of tissues from lack of oxygen or nutrients resulting from inadequate blood flow is a potent inflammatory stimulus. The edge of a recent infarct often shows an acute inflammatory response (Fantone and Ward, 1999).

According to Dennis (2003), the clinical signs of inflammation, term phlogosis by Greeks and inflammation in Latin, were described in classical times. In the second century AD, the Roman encyclopedist Aulus Celsus described the five cardinal signs of inflammation namely:

1. Redness (rubor) : An acutely inflamed tissue appears red, for example skin affected by sunburn, cellulitis caused by bacterial infection or acute conjunctivitis. This is due to dilatation of small blood vessels within the damaged area.

2. Heat (calor) : Increase of temperature on the skin is seen only in peripheral parts of the body. It is due to increased blood flow (hyperaemia) through the region, resulting in vascular dilatation and the delivery of warm blood to the area.

3. Swelling (tumor) : Swelling results from edema, the accumulation of fluid in the extra vascular space as part of the fluid exudate, the physical mass of the inflammatory cells migrating into the area.

4. Pain (dolor) : For the patient, pain is one of the best known features of acute inflammation. It results partly from the stretching and distortion of tissues due to inflammatory edema and, in particular, from pus under pressure in an abscess cavity. Some of the chemical mediators of acute inflammation, including bradykinin, the prostaglandins and serotonin, are known to induce pain.

5. Loss of function : Loss of function is a well-known consequence of inflammation. Movement of an inflamed area is consciously and reflexly inhibited by pain, while severe swelling may physically immobilise the tissues.

The signs of acute inflammation are modified according to the tissue and appearances as serous, catarrhal, fibrinous, haemorrhagic, suppurative (purulent), membranous, pseudomembranous and necrotising (gangrenous) inflammation (Vander *et al.,*1999). Acute imflammation divides into 2 stages as acute and late stage.

Early Stages of Acute Inflammation

1. Changes in Vessel Calibre : In blood vessels larger than capillaries, blood cells flow mainly in the center of the lumen, while the area near the vessel wall carries only plasma. This feature of normal blood flow keeps blood cells away from the vessel wall. Changes in the microcirculation occur as a physiological response (Ganong, 2001:b). The changes following injury which make up the vascular component of the acute inflammatory reaction were "the triple response to injury": redness, heat and swelling (Vander *et al.*, 1999). The initial phase of arteriolar constriction is transient, and probably of little importance in acute inflammation. The subsequent phase of vasodilatation may last from 15 minutes to several hours, depending upon the severity of the injury. Blood flow begins to slow again, blood cells begin to flow nearer to the vessel wall, in the plasmatic zone rather than the axial stream. This allows pavementing of leukocytes are adhered to the vascular epithelium which is the first step in leukocyte migration into the extravascular space. The slowing of blood flow which follows the phase of hyperaemia is due to increased vascular permeability, allowing plasma to escape into the tissues while blood cells are retained within the vessels. The blood viscosity is increased (Meiss, 1992).

2. Increased vascular permeability : Small blood vessels are lined by a single layer of endothelial cells. In some tissues, these form a complete layer of uniform thickness around the vessel wall, while in other tissues there are areas of endothelial cell thinning, known as fenestrations. The walls of small blood vessels act as a microfilter, allowing the passage of water and solutes but blocking that of large molecules and cells. Oxygen, carbon dioxide and some nutrients transfer across the wall by diffusion, but the main transfer of fluid and solutes is by ultrafiltration. Under normal circumstances, high hydrostatic pressure at the arteriolar end of capillaries forces fluid out into the extravascular space, but this fluid returns into the capillaries at their venous end, where hydrostatic pressure is low. However, in acute inflammation, not only is capillary hydrostatic pressure increased, but there is also escape of plasma proteins into the extravascular space. Consequently, much more fluid leaves the vessels than is returned to them. The net escape of protein-rich fluid is called exudation; hence, the fluid is called the fluid exudate (Ganong, 2001:b).

3. Formation of the Cellular Exudate : The neutrophil is the main cell to mediate the effects of acute inflammation. If tissue damage is extensive, stores of neutrophils, including some immature forms, are released from bone marrow to increase the absolute count of

neutrophils in the blood. To maintain the supply of neutrophils, growth factors derived from the inflammatory process stimulate division of myeloid precursors in the bone marrow, thereby increasing the number of developing neutrophils (Rapaport and Taetle, 1991). The normally inactive endothelium has to be activated to allow adhesion of neutrophils. Normally inactive neutrophils have to be activated to enhance their capacity for phagocytosis, bacterial killing, and generation of inflammatory mediators and neutrophils have to develop the ability to move actively, from vessels towards the area of tissue damage (Mariab, 2001) (Figure 8).
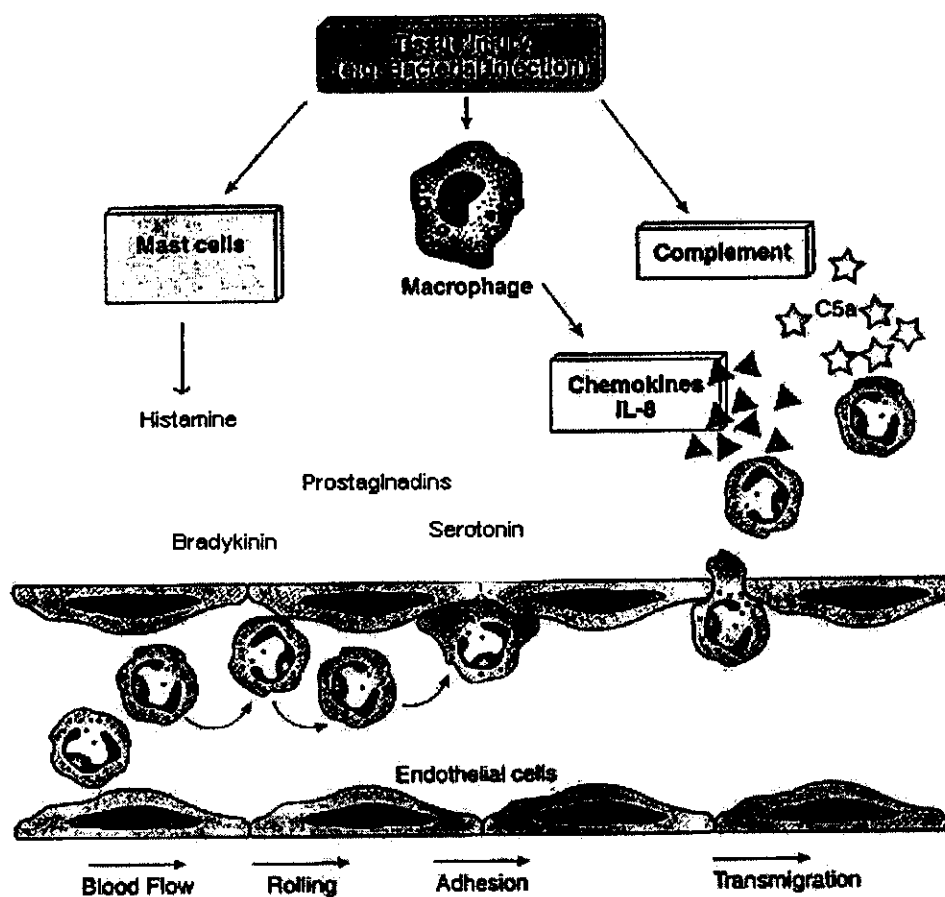
Figure 8. Regulation of leukocyte recruitment (Adapted from Fantone and Ward, 1999)

Later Stages of Acute Inflammation

The movement of neutrophils from the vessel lumen into a damaged area is mediated by substances known as chemotactic factors, which diffuse from the area of tissue damage. Migration of neutrophils occurs along a concentration gradient. The main neutrophil chemotactic factors are C5a, LTB4, and bacterial component. These factors bind to receptors on the surface of neutrophils and activate secondary messenger systems, stimulating increased cytosolic calcium, with resulting assembly of cytoskeletal specializations involved in motility. Neutrophils may arrive at sites of injury by random movement, and then be trapped there by immobilising factors that is a process analogous to the trapping of macrophages at sites of delayed-type hypersensitivity by migration inhibitory factor.

The spread of the acute inflammatory response following injury area of tissue suggests that chemical substances are released from injured tissues, spreading outwards into uninjured areas. These chemicals, called endogenous chemical mediators, cause vasodilatation, migration of neutrophils, chemotaxis and increased vascular permeability. The chemical mediators released from cells are as follows :

1. Histamine : This is the best-known chemical mediator in acute inflammation. It causes vascular dilatation and the immediate transient phase of increased vascular permeability. It is stored in mast cells, basophil and eosinophil leukocytes, and platelets (Pflanzer, 1992). Histamine release from those sites such as mast cell degranulation, is stimulated by complement components C3a and C5a.

2. Lysosomal compounds : These are released from neutrophils and include cationic proteins, which may increase vascular permeability and neutral proteases, which may activate complement (Brestel and Dyke, 1990).

3. Prostaglandins : Inflammatory cells contain specific cyclooxygenase enzyme that generate endoperoxide derivatives of arachidonic acid, including prostaglandin G_2 (PGG_2) and prostaglandin H_2 (PGH_2). The endoperoxides are unstable, and depending on the specific inflammatory cell or tissue are further metabolized to more stable prostaglandins. The latter include PGI_2 (prostacyclin), $PGF_{2\alpha}$, PGE_2, PGD_2 and thromboxane A_2 (TXA_2) (Goodman, 1992). The primary cyclooxygenase metabolite in platelet is TXA_2. Endothelial cells secrete principally PGI_2. Monocyte or macrophages, depending on their state of activation, produce any or all of these derivative products. The PGI_2 and PGE_2 having the vasodilation effects. However,

vasodilation can enhance vascular permeability at sites of inflammation. PGI_2 and PGE_2 bind to specific receptors on inflammatory cells, thereby activating adenylyl cyclase and increasing intracellular cyclic adenosine monophosphate (cAMP) levels.

4. Leukotrienes : These are also synthesis from arachidonic acid, especially in neutrophils, and appear to have vasoactive properties. SRS-A (slow reacting substance of anaphylaxis), involved in type I hypersensitivity, is a mixture of leukotrienes (Fantone and Ward, 1999).

5. 5-hydroxytryptamine (serotonin) : This is present in high concentration in mast cells and platelets. It is a potent vasoconstrictor.

6. Lymphokines : This family of chemical messengers released by lymphocytes. Apart from their major role in type IV hypersensitivity, lymphokines may also have vasoactive or chemotactic properties (Rang and Dale, 1991:b).

The following chemical mediators were found from plasma.

1. Complement system : The complement system is a cascade system of enzymatic proteins. It can be activated during the acute inflammatory reaction in various ways.

2. Kinin system : The kinins are peptides of 9-11 amino acids; the most important vascular permeability factor is bradykinin. The kinin system is activated by coagulation factor XII. Bradykinin is also a chemical mediator of the pain which is a cardinal feature of acute inflammation (Rang and Dale, 1991:b).

3. Coagulation system : The coagulation system is responsible for the conversion of soluble fibrinogen into fibrin, a major component of the acute inflammatory exudate.

4. Fibrinolytic system : Plasmin is responsible for the lysis of fibrin into fibrin degradation products, which may have local effects on vascular permeability.

The sequelae of acute inflammation depend upon the type of tissue involved and the amount of tissue destruction, which depend in turn upon the nature of the injurious agent. The possible outcomes of acute inflammation are as follows.

1. Resolution of Acute Inflammation : The term resolution means the complete restoration of the tissues to normal after acute inflammation. The sequence of events leading to

resolution is usually to phagocytosis of bacteria by neutrophils and intracellular killing, fibrinolysis, phagocytosis of debris, especially by macrophages.

2. Suppuration : Suppuration is the formation of pus, a mixture of living, dying and dead neutrophils and bacteria. Once pus begins to accumulate in a tissue, it becomes surrounded by a "pyogenic membrane" consisting of sprouting capillaries, neutrophils and occasional fibroblasts. Such a collection of pus is called an abscess, and bacteria within the abscess cavity are relatively inaccessible to antibodies and to antibiotic drugs (Guyton and Hall, 2000:b).

3. Organisation : Organisation of tissues is their replacement by granulation tissue. When the large amounts of fibrin are formed, which cannot be removed completely by fibrinolytic enzymes from the plasma or from neutrophil polymorphs, substantial volumes of tissue become necrotic or dead tissue, it is not easily digested, exudate and debris cannot be removed or discharged.

During organization, new capillaries grow into the inert material (inflammatory exudate), macrophages migrate into the zone and fibroblasts proliferate, resulting in fibrosis.

4. Progression to Chronic Inflammation : If the agent causing acute inflammation is not removed, the acute inflammation may progress to the chronic stage. In addition to organisation of the tissue, the character of the cellular exudate changes, with lymphocytes, plasma cells and macrophages replacing the neutrophil polymorphs. Often, however, chronic inflammation occurs as a primary event, there being no proceeding period of acute inflammation (Wynsberghe *et al.*, 1995).

The local effects are usually clearly beneficial, the fluid and cellular exudates may have useful effects. Beneficial effects of the fluid exudate are as dilution of toxins, entry of antibodies, drug transport, fibrin formation, delivery of nutrients and oxygen, and stimulation of immune response. But the release of lysosomal enzymes by inflammatory cells may also have harmful effects as digestion of normal tissues, swelling, and inappropriate inflammatory response.

II. Chronic Inflammation

Chronic inflammation may be a sequel to acute inflammation or an immune response to a foreign antigen. The process may become chronic if the inflammatory response is unable to eliminate the injurious agent or restore injured tissue to its normal state. Chronic inflammation primarily serves to contain and remove a pathological agent or process within a

Aspirin

This drug is the prototype of non-steroidal anti-inflammatory drugs (NSAIDs) and used for the treatment of mild to moderate pain. Aspirin (Figure 9), is more useful in the treatment of headache, neuralgia, arthralgia and other pain arising from integumental structures than in acute severe pain of visceral origin. However, it may relieve moderate postoperative, postpartum or other visceral pain (Ross and Dehoratius, 1989). If the pain is mild to moderate, aspirin may provide adequate relief and tried prior to use of opioid analgesics. Large dose that are sufficient to provide a blood salicylate concentration have an anti-inflammatory action, which may contribute to relief of pain when inflammation is a factor. When therapy is indicated to reduce fever, aspirin is one of the most effective drugs (Rang and Dale, 1991:a).
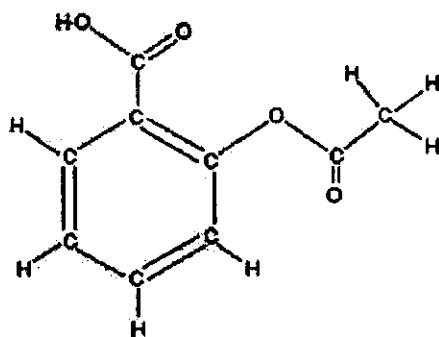
Figure 9. Structure of aspirin (Mutscler and Derendorf, 1995:b)

1. Pharmacokinetics

Aspirin is absorbed primary from the small intestine and secondary from stomach. Absorption is rapid following oral administration of conventional tablets or capsules, but the rate is affected by gastric emptying time and the release characteristics of the dosage form. Absorption is most rapid when aspirin is given in solution. Appreciable concentrations are found in plasma in less than 30 minutes after a single dose and a peak value is reached in about 1 h. Aspirin is rapidly hydrolyzed to salicylic acid before entering the systemic circulation and CNS (Ross and Dehoratius, 1989). Hydrolysis by plasma esterase is rapid and cleared by renal extraction. It is conjugated with glycine (forming salicyluric acid) and glucuronic acid (forming salicylphenolic glucoronide and salicylacyl glucoronide). A small fraction of salicylic acid is oxidized to gentisic acid. The enzymes forming salicyuric acid and salicylphenolic glucoronide are saturable and

follow Michaelis-Menten kinetics. Therefore, the pharmacokinetics of salicylate elimination are complex, since both the ratio of metabolites and clearance are dose-dependent. Approximately 70 % to 90 % of salicylic acid is bound to serum albumin and the apparent volume of distribution ranges from 0.1 to 0.35 L/kg, depending on drug concentration. The half-life of salicylate increases with the dose 3.1 to 3.2 h with 300 to 650 mg, 5 h with 1 g and 9 h with 2 g. As the dose and half-life increase, a larger portion is excreted unchanged (Jonh and Bonald, 1993).

2. Pharmacodynamics

Data from animal studies have shown that the analgesic effect of aspirin on induced pain is principally peripheral (blockade of pain impulse generation). The primary clinical effects of aspirin appear to be related to inhibit cyclooxygenase (prostaglandin synthesis) (Jonh and Bonald, 1993), since the actions of the prostaglandins have been reported to include hyperalgesia (pain), fever, edema (inflammation) and erythema. They do not inhibit 5-lipoxygenase and therefore, do not affect the formation of leukotrienes (Mutschler and Derendorf, 1995:b) (Figure 10).
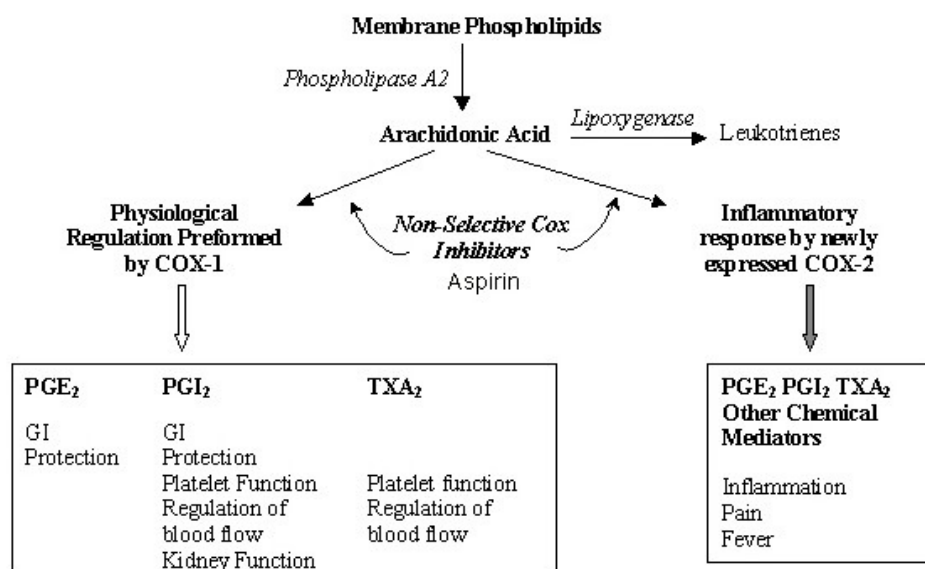

Figure 10. Mechanism of aspirin to inhibit cyclooxygenase (Vander, 2001)

3. Indication

Aspirin is used for the relief of mild to moderate pain such as headache, toothache, dysmenorrhoea and myalgias. It is also used in acute and chronic inflammatory disorders such as rheumatoid arthritis and osteoarthritis. In the treatment of minor febrile conditions, such as colds or influenza, aspirin is of value for the reduction of temperature. It is also used in the prevention of arterial and venous thrombosis (Aitchison *et al.*, 1993:a).

4. Adverse Reactions

Although some of the therapeutic actions of these drugs may be related to the inhibition of prostaglandin synthesis, many adverse reactions also are due to this pharmacologic property. Generally, serious adverse response are associated with long-term drug use, but a few life-threatening reactions have been reported after a single exposure to the drug (Brestel and Dyk, 1997).

4.1. Gastrointestinal : The severity of gastrointestinal side effects is related to dosage, frequency of use and alcohol intake. However, there is concern that aspirin may aggravate damage in patients with pre-existing inflammatory bowel disease. To minimize injury, patients receiving large doses or prolonged therapy should be asked to report black or bloody stools or faintness promptly. Such patients should be monitored for signs and symptoms of ulceration and bleeding (Day *et al.,* 2000). Although concomitant use of antacids usually prevents injury, the resulting alkalization of the urine may reduce the serum concentration of aspirin below an effective level. Misoprostol which is a synthetic prostaglandins may prevent peptic ulcers when used with aspirin (Kunn, 1991).

4.2. Renal : Adverse renal effects with even continuous use are uncommon. Nevertheless, since renal failure may develop, particularly in high-risk patients and the elderly, renal function should be assessed periodically with use of these drug. Aspirin may produce sodium and water retention with edema initially but this effect is transient. Sodium restriction, concurrent diuretic use, and conditions that diminish the circulatory volume of otherwise increase endogenous vasoconstrictor release in renal disease, make the kidney dependent on vasodilator prostaglandins to maintain adequate renal blood flow (Kvam and Swingle, 1990). If prostaglandin synthesis is inhibited by this analgesic, renal insufficiency due to hypoperfusion or acute tubular necrosis may result. Inhibition of prostaglandin production can lead to hyperkalemia, particularly

in the presence of renal insufficiency or diabetes or with the coadministration of a potassium-sparing diuretic. An interstitial nephritis, usually associated with nephritic syndrome, has been reported with use of aspirin. Usually patients showed proteinuria that may suggest nephrotoxicity, hypoalbuminemia and edema. The long-term use of aspirin can produce a papillary necrosis attributed to impaired blood supply to the renal medulla. Microscopic or gross hematuria suggests developing papillary necrosis (Jonh and Bonald, 1993).

4.3. Hepatic : Aspirin administered regularly in doses greater than 50 mg/kg can produce mild and reversible hepatic damage. This is usually manifested as an increase in aminotransferase values but biopsies reveal focal hepatocellular necrosis, hepatocytic swelling, intracellular and extracellular acidophilic bodies and portal inflammation. A small number of patient experience more severe hepatic damage with jaundice, prolonged prothrombin time with bleeding or intravascular coagulation. Aspirin also may precipitate hepatic encephalopathy in patients with chronic liver disease. The hepatotoxicity generally occurs only after several months of treatment and appears as cholestatic jaundice with markedly elevated values in hepatic function tests and histologic evidence of necrosis, portal infiltrates and cholestasis (Foegh and Ramwell, 2001).

4.4. Hypersensitivity : Two distinct nonimmunologic syndromes characterized by bronchospasm and rhinitis or angioedema and urticaria may follow a single dose or may occur in patients who previously received this drugs without incident.

4.5. Hematologic : Aspirin exerts a pronounced inhibitory platelet aggregation. This effect is more prominent in patients with inborn disorders of platelet function in Von Willebrand or Bernard-Soulier disease, and in patients receiving heparin or oral anticoagulants. For most NSAIDs were inhibited platelet agrregation is reversible, but inhibition by aspirin is irreversible (Schuna and Coulter, 1993).

4.6. Pregnancy and Lactation : Aspirin has been examined extensively for their potential adverse effects on the pregnant woman, the fetus and on the nursing neonate whose mother is receiving aspirin. It is presumed that, like aspirin, prolong gestation and labor, increase maternal blood loss during delivery and may cause fetal intracranial hemorrhage. Fetal growth retardation may be related to inhibition of glucose-induced insulin release. Large dose of aspirin in the mother can induce bleeding or rash in nursing infant (Foegh and Ramwell, 2001).

5. Intoxication

Acute aspirin intoxication is characterized initially by hyperventilation, headache, mental confusion, nausea, sweating and thirst. More severe intoxications may include convulsions and coma, skin eruption and clinically significant acid-base disturbance. Carbon dioxide is exhaled in excess during hyperventilation and results in respiratory alkalosis (Ross and Dehoratius, 1989). Increased renal elimination of bicarbonate compensates for respiratory alkalosis. Metabolic and respiratory acidosis is seen in severe salicylate intoxication. This result from salicylates displacing plasma bicarbonate, impaired renal function with metabolic acid accumulation and uncoupling oxidative phosphorylation with organic acid accumulation. Severe acidosis is more commonly seen in children and infants due to the toxic dose of aspirin. Therapy for aspirin intoxication is primarily supportive with the first measure to reduce absorption from the gastrointestinal tract and, second, to restore the acid-base balance. Treatment includes sodium bicarbonate infusion to increase alkali reserves and increasing urinary pH to augment the renal elimination of salicylate. Life-threatening intoxications may require hemodialysis (Colasanti, 1990:a).

6. Drug Interactions

Because aspirin is widely used, its interaction with other drug must be considered. Large dose of aspirin taken for several days could inhibit platelet aggregation, patient receiving oral anticoagulants should be instruct to avoid. In noninsulin-dependent diabetics, aspirin decrease the blood glucose concentration by inhibiting prostaglandins synthesis and may enhance the effect of the oral hypoglycemics. So, This drug should not be given hypoglycemic agent. In addition, it have a uricosuric effect, cause uric acid retention. Patients with gout should avoid aspirin (John and Bonald, 1993).

Morphine

Morphine (Figure 11), one of the oldest medicine known was the first alkaloid to be isolated in pure form. This was accomplished in 1806s by Serturner, who named his compound after the Greek god of dreams Morpheus. Morphine is obtained from opium which is the dried sap of the unripe fruit capsules of the poppy plant (*Papaver somniferum*). A number of alkaloids are present in the plant into 2 categories : phenanthrenes and benzylisoquinolines (Martin, 1990). The phenanthrenes in opium include morphine (about 10 %) and codeine (about 0.5-1 %). The benzylisoquinolines include paparvine, an alkaloid with vasodilator and antispasmodic properties but lacking analgesic properties. Morphine is the prototype of opioid agonist use as strong analgesics (Baumann, 1993).
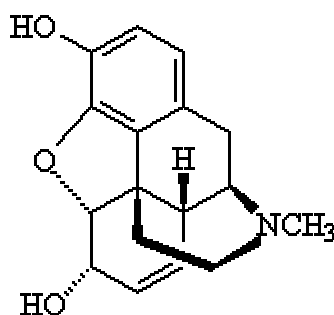

Figure 11. Structure of morphine (John and Bonald, 1993)

1. Phamacokinetics

Absorption of morphine from the gastrointestinal tract is relative slow. The volume of distribution is 3.2 ± 0.3 L/kg, the elimination half-life is 2.9 ± 0.5 h and the clearance rate is 14.7 ± 0.9 ml/min/kg. Furthermore, there is significant first-pass effect. Elderly patients may be more sensitive to morphine and have higher and more variable serum level than younger patients (Martin, 1990). Age should be considered when determining the dose and dosing interval. In infant under 1 week, the elimination half-life is prolonged to 6.8 h and the clearance is less than 50 % that of order infants (6.3 ml/min/kg). The response to morphine may be enhanced in patients with uremia, various renal disorders and renal ischemia. This may be due to accumulation of an active metabolite, morphine-6-glucoronide that is eliminated by kidney (Jaffe and Martin, 1990).

The mean elimination half-life and clearance of the parent drug are similar in patients with renal failure and in normal subjects.

2. Pharmacodynamics

Endogenous polypeptides that bind to opioid receptor sites at the presynaptic nerve terminal, and mimic some of the action of opioid have been found in the brain and other tissue. The first polyoeptides that were isolated and sequenced were two pentapeptides, met (methionine)-enkephalin and leu(leucine)-enkephalin (John, 1990). A larger peptide with similar activitiy, beta-endorphine is present in the pituitary and arcuate body of the hypothalamus. Different type and subtype of opioid receptor have been postulated to explain the various actions of the opioids. The μ (mu) receptor mediates morphine-like analgesia, respiratory depression, miosis, reduction of gastrointestinal motility and euphoria. The κ (kappa) receptor probably mediates pentazocine-like analgesia. The σ (sigma) receptor may , together with a phencyclidine site, mediate psychotomimetic effects produced by pentazocine and other agonist-antagonist. The δ (delta) receptor also as has been found in the CNS and is selective for enkephalins (Smith, 1995). Analgesic agents acting at the supraspinal, spinal level presumably interact with μ, κ and δ receptor. All three recetors belong to the superfamily of G-protein coupled receptors with the characteristic seven transmembrane-spanning regions. Receptors are coupled to adenylyl cyclase through G_i, and probably to other second-messenger systems as well. Activation of the three opioid receptors decreases synthesis of cyclic adenosine monophosphate (cAMP), increase K^+ conductance, and decrease Ca^{2+} conductance. Change in K^+ and Ca^{2+} conducetance are inhibitory to neuronal activity. So, morphine activated on opioid receptors usually results in decreased to release of excitatory neurotransmitter and neuronal transmission (Substance P) that cause pain (Brown, 1979; Stephen, 1998) (Figure 12).
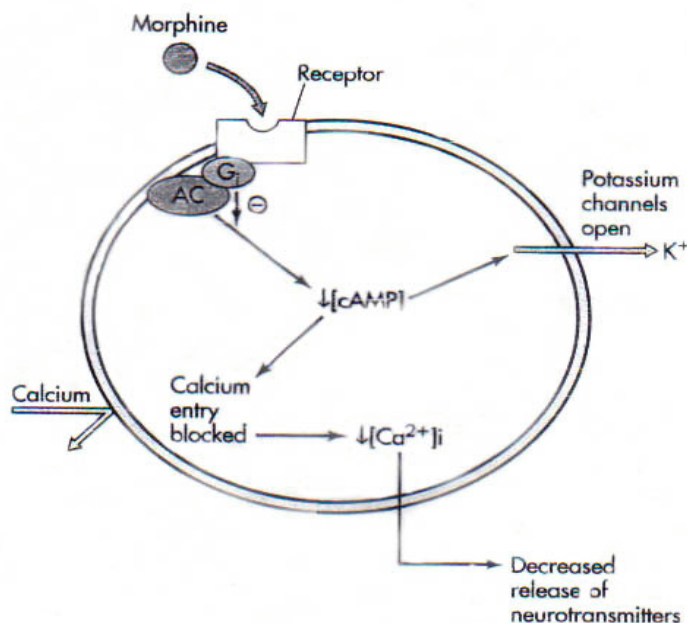
Figure 12. Mechanism of morphine on opioid receptors (Stephen, 1998)

3. Indication

3.1 Acute pain : Morphine is indicated for relief of moderate to severe acute pain. When administered systemically, it alter the psychological response to pain as well as the nociceptive sensation. It act on higher centers of the CNS to produce analgesia without loss of consciousness. Morphine is used for short-term therapy for serve, acute pain (trauma, burns, surgery) (Bonica, 1980).

3.2 Chronic pain : The treatment of chronic pain of nonmalignant origin depends on its cause and severity. The selection of opioid should be based on the severity of the pain and patient's response. Usually, therapy is initiated with an opioid such as codeine plus a salicylate or acetaminophen. The morphine preparation should not be used primarily to relieve anxiety or depression. Neuropathic pain may follow injury to peripheral nerves, spinal cord, soft tissue or visceral structure. The injury may be caused by compression, surgery, viral infection or neoplastic disease (Meed *et al.*, 1987). Neuropathic pain is typically a dysesthesia (abnormal burning, shooting pain) that less responsive to opioid analgesics than other types of pain. Nonopioid drugs, including selected antidepressants and anticonvulsants, may be useful.

4. Adverse Reactions

Morphine causes adverse reactions that limit their usefulness such as respiratory depression, nausea, vomiting, constipation, orthostatic hypotension, urinary retention, diaphoresis, pruritus, sedation, confusion, constipation. Stimulant laxatives counteract the opioid-induced reduction in bowel motility. Morphine-induced neusea and vomiting occasionally persist beyond this period and prolonged antiemetic therapy or substitution of an alternative drug may be required (Stephen, 1998). Morphine also can decrease gastric emptying. During surgery, delayed gastric emtyping can result in retention of secretions and create the potential for aspiration. Other reactions include miosis, spasm of the biliary and urinary tracts and rarely, inappropriate secretion of antidiuretic hormone and hypersensitivity phenomena such as urticaria, rash and anaphylactic reactions with intravenous administratrion. Respiratory depression is the most dangerous acute reaction produced by the morphine-like analgesics, although it is rarely severe with usual doses. Morphine decrease the respiratory rate, tidal volume and minute ventilation and decrease the sensitivity to carbon dioxide (Benedetti and Butler, 1990). Serve hypoventilation or apnea is most likely to develop in elderly debilitated patients and in those with respiratory disorders characterized by chronic hypoxia.

Morphine should be given in reduced doses or withheld from patients in shock or those decreased blood volume for severe hypotension may develop. Because it may cause hypoventilation, the resulting hypercapnia produces cerebrovascular dilation and increased intracranial pressure therefore, it must be used with extreme caution in patients with head injuries, intracranial lesions or tumors or other conditions in which increased intracranial pressure should be avoided because morphine may produce miosis, use in patients with suspected head injuries or in those undergoing intracranial surgery may mask the dilation of one or both pupils that is an important sign of increased intracranial pressure (Stephen, 1998). Morphine decrease urine production directly by acting on the kidney and indirected by stimulating the release of antidiuretic hormone. The most important under adverse effects of morphine are psychological and physical dependency as well as tolerance development. The non-medical stress use of opioids presents the primary problem for addiction. It is used to induce euphoria and the extremely unpleasant withdrawal symptoms are usually ignored by illicit drug users. Morphine addicts quickly tolerate higher doses, up to 1 g morphine daily. The mood of morphine addicts is labile and a pale yellow pallor reflects their generally poor health. In case of advanced addiction,

symptoms include insomnia, weight loss, impotence, tremor, coordination problems and psychiatric disorders. If the addict cannot maintain opioid blood level, the first symptoms of restlessness, depression, anxiety, freezing or sweating as well as increased lacrimation occur within hours. After 24-48 h, withdrawal symptoms peak with nausea, vomiting, diarrhea, dehydration and increased respiration, heart rate, systolic blood pressure and temperature present (Smith, 1995). Furthermore, muscle spasms and abdominal cramping occur. Administration of morphine antagonists also causes similar symptoms in addicts. Methadone programs attempt to reduce drug crime by oral administration of *l*-methadone and controlling withdrawal symptoms (Baumann, 1993).

5. Intoxication

Acute morphine intoxication is characterized by deep coma with shallow breathing and maximum pupillary constriction. The typical triad of symptom for morphine overdosing is coma, respiratory depression and miosis. Symptoms may also include cyanosis, cold skin and hypothermia (Benedetti and Butler, 1990). Death is due to respiratory failure. The lethal dose of morphine in a nonaddict is 100 mg parenterally and 300-1,500 mg orally. For an infant, 2-3 drops of tincture of morphine can be deadly. Restoring oxygen is essential in treating morphine intoxication as well as hypnotic intoxication. Besides cardiopulmonary resuscitation, the use of opiate antagonist naloxone has been successful. The initial dose is 0.4-2 mg i.v., i.m. or s.c. and may be followed every two to three minutes with 0.4-2 mg. In addicts, the doses need to be reduced due to the risk of dangerous withdrawal symptoms and dosing intervals are shortened.

6. Drug Interactions

The dose of morphine should be reduced in patients receiving other drugs that depress the CNS such as antipsychotic agents, barbiturates, antianxiety agents or the dose of the latter agent should be adjust. Severe adverse reactions have occurred following the administration of meperidine to patients receiving monoamine oxidase inhibitors (Colasanti, 1990:b).

Naloxone

        The pure opioid antagonist drug, naloxone (Figure 13) is a morphine derivative with bulkier substituents at the N position. One structure change that converts a narcotic agonist to an antagonist is alkylation of the piperidine nitrogen. For example, when the methyl group on the piperidine nitrogen of morphine is replaced by the unbranched three-carbon side chain (such as propyl, allyl or isopropyl), the compound becomes a narcotic antagonist. Naloxone has a relatively high affinity for opioid binding sites of the μ receptor type. Their affinity for the other receptors such as κ and δ receptors are found in both supraspinal and spinal sites (Colasanti:b ,1990; Smith, 1995).
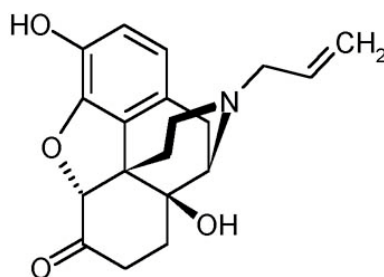

Figure 13. Structure of naloxone (Colasanti, 1990:b)

1. Pharmacokinetics

        Naloxone has poor efficacy when given by the oral route and a short duration of action about 1-4 hours when given by injection. It is usually given intravenously and its effect are produced immediately. It is rapidly metabolish by the liver. Metabolic disposition is chiefly by glucoronide conjugation (Rang *et al*., 1999:b). (Table 4.)

2. Pharmacodynamics

        Naloxone is capable of antagonizing the effects produced by narcotics at μ, κ and δ receptors. The affinity of the antagonist for the μ receptor is 10-20-fold greater than for the κ and δ receptor sites (Colasanti:b, 1990). When given to a morphine-treated subject, the antagonist will completely and dramatically reverse the opioid effects within 1-3 minutes. The patients who are acutely depressed by overdose of an opioid, the antagonist will effectively

normalize respiration, level of consciousness, pupil size, and bowel activity (Way and Way, 1992).

3. Indication

Naloxone is the drug of choice for narcotic overdose. It is very important that the relatively short duration of action of naloxone be born in mild because a severely depressed patient may recover after a single dose of naloxone and appear normal, only to relapse into coma after 1-2 hours. The usual dose of naloxone is 0.1-0.4 mg intravenously, which can be repeated as necessary (Way and Way, 1992).

4. Adverse Effects

Nausea and vomiting have occurred and there have been individual reports of hypotension, hypertension, cardiac arrhythmias, and pulmonary edema, generally in patients given naloxone postoperatively. Seizures have been reported infrequently (Aitchison *et al*., 1993:b).

Table 4. Narcotic Analgesic Pharmacokinetics (Terry, 1993)

Agent	Time to peak (h)	Half-life (h)	Analgesic onset (min)	Analgesic duration (h)
Morphine	0.5-1	2-4	15-60	4-5
Levorphanol	0.5-1	12-16	30-90	4-5
Pentazocine	0.25-1	4-5	15-20	3
Naloxone*	0.5-2	0.5-1.5	2-5	0.5-1
Naltrexane*	1	4-13	15-30	24-72

Based on intramuscular data unless other wise indicated.

*Drug Antagonist

tissue (Fantone and Ward, 1999). The cellular components of the chronic inflammatory response are described as following :

The macrophage is the pivotal cell in regulating the reactions that lead to chronic inflammation. The accumulation of macrophages mainly reflects the recruitment of circulating monocytes by chemotactic stimuli and their differentiation in tissues. The local proliferation of resident tissue macrophage may also contribute. In addition, macrophages regulate lymphocyte response to antigens and secrete other mediators that modulate the proliferation and function of fibroblasts and endothelial cells (Stanier and Forsling, 1990).

Plasma cells also participate in the chronic inflammatory response. These lymphoid cells, which are rich in rough endoplasmic reticulum are the primary source of antibodies. The production of antibody to specific antigens at sites of chronic inflammation is important in antigen neutralization, clearance of foreign antigens and particles and antibody-dependent cell-meadiated cytotoxicity (Fantone and Ward, 1999).

Lymphocytes are a prominent feature of chronic inflammatory reactions and perform vital functions in both humoral and cell-mediated immune responses. T lymphocytes not only function in the regulation of macrophage activation and recruitment through the secretion of specific mediators (lymphokines) but also modulate antibody production and cell-mediated cytotoxicity (Rang and Dale, 1991:b). Recently, natural killer cells and specifialized forms of lymphocytes as T cells, CD5 B cells, have been implicated as participants in the defense against viral and bacterial infections. Their activity does not require previous sensitization to foreign antigens.

Eosinophils are occasionally a conspicuous component of the chronic inflammatory response. They are particularly evident during allergic-type reactions and parasitic infestations. Eosinophils share many functional features with the neutrophil. Their rhomboid, cystalloid granules are rich in acid phosphate and have a specific peroxidase activity. The precise role of eosinophils in chronic inflammatory reactions is less clear (Robert, 2003).

Polymorphonuclear leukocytes, although characteristic of acute inflammation may also be observed at sites of chronic inflammation.