CHAPTER IV

DISCUSSION AND CONCLUSION

CHRONIC EFFECT OF PARACETAMOL

An important finding in the present study was that chronic administration of paracetamol could alter central 5-HT system by down-regulating the 5-HT_{2A} receptors at post-synaptic membrane and up-regulating the 5-HT uptake sites at pre-synaptic membrane in frontal cortex of rat brain. Interestingly, the degree of receptor down-regulation and uptake site up-regulation became less evidenced after administration of paracetamol for longer period. A concomitant increasing of platelets 5-HT concentrations was also observed in chronic administration of paracetamol for 15 days, but not found in 30-day treatment. On the other hand, the concentrations of 5-HIAA, major metabolite of 5-HT, in platelets increased in 30-day treatment, but not found in 15-day treatment. These biochemical changes were also coincided with the changes in analgesic efficacy as well as rat body weight. The increase in tail flick latency was observed after administration of paracetamol at a dose of 400 mg/kg/day for 15 days, but not 30 days,. Moreover, the decrease of body weight was found after administration of 300 and 400 mg/kg/day of paracetamol for 15 and 30 days.

These results agreed with the previous report indicating that chronic treatment with phenazone produced the decrease in the number of serotonin receptors in rat cortical brain membrane by Pini et al. (1994). The data reported herein suggested a

possible correlation between the modification of the central serotonergic system following drug administration and the analgesic activity in tail flick test; the increasing of analgesic activity associated with the elevation of 5-HT levels. Consequently, the alterations in serotonergic concentrations may induce the down-regulation of 5-HT_{2A} receptors and up-regulation of 5-HT uptake sites in 15-day paracetamol administration.

Pini et al.(1996) found that the concentrations of paracetamol in rats and mice, evaluated 90 min after administration, were relatively high compared with those found in humans after therapeutic administration but were below the toxic levels (Granados-Soto et al., 1993; Hunskaar and Hole, 1987); other studies have also shown that such doses are necessary to induce antinociceptive effects in rodents (Hunskaar et al., 1986; Pelissier et al., 1995). Moreover, Pini et al. (1994) found that the spontaneous motor activity of the rats treated with the high doses of paracetamol was not affected.

Several experiments lend additional indirect support to a central site of action of analgesic drugs. For example: sodium salicylate suppressed the escape responses elicited by electrical stimulations of the lateral hypothalamus in rats when given subcutaneouly (Dubas and Parker, 1971). Similarly, paracetamol was shown to depress the activity in single neurons in the rat thalamus evoked by electrical stimulations of afferent C-fibers (Carlsson et al., 1988). These findings were corraborated by studies in human volunteers. A single oral dose of about 1 g of aspirin influenced pain-related cerebral potentials in response to non-inflammatory noxious stimuli (Bromm et al., 1991; Chen and Chapman, 1980).

In this study, paracetamol could display antinociception by elevation of pain threshold. This was consistent with many reports. In an early experimental study in humans, paracetamol was found to elevate pain threshold caused by cutaneous heat irradiation (Flinn and Brodie, 1948). In this way, very low doses of paracetamol influenced in a dose-related manner the hyperalgesia associated with intraplantar injections of carrageenin into the rat paws (Ferreira et al., 1978). Intrathecal administration of paracetamol and a variety of NSAIDs, including indomethacin, flurbiprofen, ibuprofen, ketorolac, zomepirac, and aspirin produced a dose-dependent suppression of the hyperalgesic component of the second-phase of the formalin test in the rat (Malmberg and Yaksh, 1992a). Interestingly, 100 to 1000 times higher doses were required to produce the same effect after systemic administration (Malmberg and Yaksh, 1992a).

Paracetamol-mediated analgesia via the central mechanisms is probably the result of its ability to cross the intact blood-brain barrier in large amounts. This was reported in animals (Ochs et al., 1985) as well as in humans (Bannwarth et al., 1989; 1992b). Equilibrium was reached within a few hours, and further cerebrospinal fluid (CSF) concentrations were close to the unbound plasma concentrations. This central nervous system concentration-time profile was very similar to the analgesic profile observed in the study by Pierre et al., 1991.

It was shown that an intravenous infusion of paracetamol 1 g (Piletta et al., 1991) produced a significant increase in both the subjective pain and the R-III reflex thresholds in comparison with placebo in healthy volunteers. Interestingly, the time-analgesic effect curve of paracetamol resembled that of its concentration-time profile in the human CSF (Piletta et al., 1991; Bannwarth et al., 1992). An intramuscular dose

of indomethacin, 50 mg, was found to exert a significantly more depressive effect on the amplitude of the RIII reflex than a placebo in patients suffering from chronic low back pain or lumbosciatica (Guieu et al., 1992). In contrast, intravenous administration of 1 gm of acetylsalicylic acid had no antinociceptive influence on either the R-III reflex or the subjective pain thresholds (Piletta et al., 1991).

Despite conflicting results, several lines of evidence have accumulated to indicate that paracetamol displays a direct analgesic effect at segmental or supra-segmental levels of the CNS, as do other kinds of non-opiate analgesics, such as aspirin-like drugs, nefopam, flupirtine (Bannwarth et al., 1992a).

Some experiments are in favour of an intervention at the segmental level. Substance P intrathecally administered in mice elicited a pain-related behavioural response which was reduced by systemic pretreatment with paracetamol (Hunskaar et al., 1985). It was postulated that paracetamol might act by interfering with the function of the substance P receptors or by inhibiting neurons excited by substance P (Hunskaar et al., 1985).

Numerous studies have emphasized the crucial role of supraspinal structures (Bannwarth et al., 1993; Brune et al., 1992). Intravenous ketoprofen did not display any significant effect on the R-III reflex in paraplegic patients with a complete spinal section of traumatic origin. Conversely, it provided a clear depressive effect in normal subjects (Willer et al., 1989). Systemic paracetamol were found to reduce the firing discharge of thalamic neurons in rats evoked by the electrical stimulation of nociceptive afferents in the sural nerve without influencing the activity in ascending nociceptive pathways in the spinal cord (Carlsson et al., 1988). A dose-dependent

antinociceptive effect in visceral pain model has been demonstrated after microinjections of diclofenac into several brain regions in rats (Bjorkman et al., 1992). These findings are compatible with an activation of descending inhibitory pathways. As a result, nociceptive inputs are blocked in the spinal cord so that do not reach higher centers (Andersson and Yokata, 1987).

Central serotonergic systems involved in paracetamol-mediated antinociception has been hypothesized (Pelissier et al., 1994; Tjϕlsen et al., 1991). The analgesic activity of paracetamol was altered in rats in which the serotoninergic pathways were lesioned with intrathecal 5,6-dihydroxytryptamine (Tjϕlsen et al., 1991). Furthermore, the effect of intrathecal paracetamol in the paw pressure test was abolished by intrathecal tropisetron, a 5-HT_3-receptor antagonist injection (Pelissier et al., 1994).

This hypothesis was reinforced by several experiments. As the analgesia induced by intrahypothalamic microinjections of aspirin in conscious monkeys was antagonized by pretreatment with either serotonergic or catecholaminergic receptor blockers, it was suggested that aspirin might activate monoaminergic control systems (Shyu and Lin, 1985). Similarly, the central analgesic effect of aspirin in rats was counteracted by pretreating the animals with metergoline, a serotonin receptor antagonist, but not by the opioid receptor antagonist naloxone (Groppetti et al., 1988). Moreover, the administration of either of the 5-HT precursor compounds, tryptophan or 5-HTP also inhibited the neural activity evoked by noxious stimulation in addition to increasing the turn over of 5-HT in brain. These observations are consistent with the view that a 5-HT, but not a naloxone-sensitive opioid mechanism, may be relevant for acetylsalicylate or salicylate-mediated analgesia (Longheu et al., 1988).

Taber and Latranyi (1981) evaluated the ability of para-chlorophenylalanine (PCPA), an inhibitor of 5-HT biosynthesis, to antagonize the antinociceptive effects of morphine (a μ-agonist), pentazocine (a mixed agonist-antagonist) All drugs dose-dependently increased latency to struggling in response to a linear in pressure applied to the yeast-inflamed paw. In each case this effect was abolished by pretreatment with PCPA but reversed by administration of the 5-HT precursor 5-HTP, which restores central 5-HT levels by circumventing PCPA blockade of tryptophan hydroxylase. The anti-analgesic action of PCPA could not be attributed to a hyperalgesic effect because PCPA alone did not alter the reaction time of the non-inflamed or inflamed paw. Further, the action of PCPA could not be related to an interaction with inflammatory mechanisms because its anti-analgesic effect against morphine-induced antinociception was similar for both the normal and inflamed paws. It only antagonised the antinociceptive but not the antioedema effects of the NSAID, clonixin. Assigning a standard potency of 1.0 to dose responses determined in control animals, PCPA antagonized the analgesic response to morphine in both paws and to ASA in the inflamed paw to approximately the same degree. These observations suggest that a common mechanism is involved in modulating the antinociceptive activity of drugs which are characterised by different mechanisms and sites of action. The reversal of the anti-algesic effect by 5-HTP given either before or after the analgesics indicates that the effect is not related to any PCPA-induced change in drug metabolism, but is strong evidence in support of an effect mediated by changes in 5-HT levels.

In the CNS, 5-HT neurons are involved in nociceptive transmission as well as in the pain inhibition induced by opiate agonist (Bensemana and Gascon, 1978; Lin et

al., 1980a,b; Messing and Lytle, 1977). CNS pathways of 5-HT, in particular projecting to the spinal cord, can mediate antinociception and are involved in the expression of the antinociceptive actions of opioids such as morphine (Basbaum and Fields, 1984; Le Bars, 1988; Sawynok, 1989). Indeed, 5-HT turnover can be modulated by noxious stimuli and a spinal action of 5-HT can both induce behavioural antinociception and inhibit dorsal horn neurons responsive to noxious stimulation (Besson and Chaouch, 1987; Le Bars, 1988; Roberts, 1990; Solomon and Gebhart, 1988).

Several investigators have demonstrated that intrathecal administration of 5-HT alters nociceptive sensitivity in a variety of different animal species (Wang, 1977; Yaksh and Wilson, 1979; Archer et al.,1985; Minor et al., 1985). Early studies performed by Wang (1977) showed that intrathecal administration of 5-HT blocked the tail flick response to noxious heat and shortly after Yaksh and Wilson showed that methysergide could reverse this effect when given systemically.

It is well known that 5-HT in gray matter of the spinal cord is associated with terminal systems deriving from cell bodies located in the caudal raphe nuclei (Dahlstrom and Fuxe, 1965; Basbaum et al., 1976). Two lines of evidence suggest that this descending serotonergic system mediates an inhibition of spinal function resulting in behaviourally defined changes in the nociceptive threshold. First, activation of this descending system by electrical stimulation in the vicinity of the raphe nuclei produces an inhibition of dorsal horn cells responsive to nociceptive input, obtunds spinal reflexes and produces apparent increases in the nociceptive threshold of the intact animals (Clineschmidt and Anderson, 1970; Proudfit and Anderson, 1975; Oliveras et al., 1975; Beall et al., 1976; Basbaum et al., 1977; Fields et al., 1977).

Such inhibitory effects have been reported to be antagonized by the systemic administration of several putative 5-HT antagonists such as lysergic acid diethylamide, methysergide and cinanserin (Engberg et al., 1968; Clineschmidt and Anderson, 1970; Gunbaud et al., 1973; Proudfit and Anderson, 1974). The observation that electrical activation of the raphe spinal system inhibits spinal activity correlates well with iontophoretic experiments showing that 5-HT inhibits the response of dorsal horn cells evoked by nociceptive stimulation (Randic and Yu, 1976; Headley et al., 1978). Moreover, it has been demonstrated that morphine injected into the central gray can produce a profound depression of nociceptive neurons in the dorsal horn (Bennett and Mayer, 1976; Ruda et al., 1976), block reflex activity and produce a clear elevation in the nociceptive threshold of the intact and behaving animal (Yaksh and Rudy, 1978).

The antinociceptive effects of spinally administered 5-HT are well established (Headley et al., 1978; Wang, 1977; Yaksh and Wilson, 1979). Spinal 5-HT probably mimics the activity of 5-HT containing fibers descending from neurons located in the brain stem raphe nuclei, electrical stimulation of which also produces antinociceptive effects in awake animals (Watkins et al., 1982) and inhibition of responses to noxious stimulation of the skin in single dorsal horn neurons (Rivot et al., 1980). The 5-HT antagonist methysergide has been shown to reverse the antinociception produced by spinal 5-HT in addition to producing hyperalgesia in rats when used intrathecally alone (Glaum et al., 1990; Zemlan et al., 1983). Many experiments imply that 5-HT receptors are involved in spinal antinociception.

Controversy exists about the possible role played by the 5-HT_1, 5-HT_2 and 5-HT_3 receptors in the modulation of pain. In the tail flick test, intrathecal administered

5-HT_{1A} antagonists did not alter (Crisp et al., 1991) or produce a dose-related blockade (Xu et al., 1994) of 5-HT-induced antinociception. Intrathecal administration of 5-HT_{1A} agonists has been reported to facilitate (Crisp et al., 1991; Alhaider and Wilcox, 1993), to inhibit (Eide and Hole, 1991; Xu et al., 1994) or to not modify pain reactions (Solomon and Gebhart, 1988; Mjellem et al., 1992; Millan, 1994). A similar degree of controversy exists concerning the possible role played by the 5-HT_2 receptors and 5-HT_3 receptors. Activation of the 5-HT_2 receptors has been reported to facilitate (Eide and Hole, 1991) or to inhibit (Solomon and Gebhart, 1988) the transmission of nociceptive impulse. Antinociceptive 5-HT_2 receptors have a supraspinal location, but seem to influence descending inhibitory systems, besides affecting supraspinally organized behavioural responses. Thus, the excitatory action of 5-HT on nucleus raphe magnus cells and the antinociceptive effects of 5-HT microinjected into nucleus raphe magnus, reported by Dickenson et al.(1979) are probably due to an effect mediated by 5-HT_2 receptors (Llewelyn, et al., 1984). According to Glaum et al., (1988, 1990), spinal 5-HT_3 receptors mediated the antinociceptive effects of intrathecal administered 5-HT. In contrast, the spinal 5-HT_3 receptors were not involved in this response, as demonstrated by Xu et al.(1994).

The activation of 5-HT_{2A} receptors facilitated nociceptive transmission might explain an antinociceptive efficacy of paracetamol in this study. This suggestion well corresponded with the reduction of 5-HT_{2A} receptors and concomitantly the elevation of pain thresholds as observed after 15-day daily administration of paracetamol. Additionally, it was confirmed by our recent observation that administration of 1,(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI), a specific 5-HT_{2A} receptors agonist,

significantly decreased pain threshold in rats as measured by tail flick test (Ruangpattanatawee, thesis data, 1998).

Patterns of 5-HT receptors distribution in the central nervous system are complex and depend on subtypes of receptor. 5-HT_2 receptors reveal a specific distribution in many brain areas including the frontal cortex (Leysen and Powels, 1990), and the cortex is one of the most important axonal projection targets for neurons derived from brain stem. Actually cerebral cortex presents highest density of 5-HT_2 receptors. The presence of very high densities of these receptors in the neocortex, especially over the pyramidal cell layers, which receive afferents from several central structures, suggest their involvement in the regulation of many brain functions, including nociceptive modulation. The reduction in the number of 5-HT_{2A} receptors in the cortical, but not in the pontine area in this study, could depend on the different density of receptors in these areas and would emphasize the role of the cortex as the end terminals for the serotonergic antinociceptive system.

Mechanisms by which paracetamol induces 5-HT_{2A} receptors plasticity are not fully understood. It has been recently shown that paracetamol has no binding affinity to either 5-HT receptors or transporter (Raffa and Codd, 1996). Since there is no evidence that paracetamol acts directly on any subtypes of 5-HT receptors, the plasticity of such receptors should be resulted from other indirect interaction. Changes in concentration of neurotransmitter has a significant impact on receptor adaptation. To prove the possibility of this hypothesis, the levels of 5-HT concentrations were measured in platelets. Platelets have long been used as an experimental model for serotonergic neurons. In fact, platelets and serotonin neurons show many common characteristics including embryological ancestry and the presence of [^{3}H]imipramine

and 5-HT_2 binding sites as well as MAO and neuron-specific enolase. Thus the measurement of platelet 5-HT and 5-HIAA concentrations may provide a "window" to the brain. It has been shown that 15-day administration of paracetamol could increase the level of 5-HT in platelets in this study. Therefore, we may assume that paracetamol, by increasing the concentration of the 5-HT, may induce an adaptive down-regulation of the post-synaptic 5-HT_{2A} receptors.

Many findings have highlighten the complexity of the adaptive mechanisms of the 5-HT system, but the monoamine adaptation theory implies that a persistent exposure to agonist or endogenous neurotransmitters results in receptor down-regulation. Chronic administration of a more selective 5-HT_2 receptors agonist, such as DOI, has been shown to decrease 5-HT_2 receptor density (Bukholtz et al., 1988; Mc Kenna et al., 1989).

The pattern of paracetamol-induced 5-HT_{2A} receptors adaptation observed in this study is of interest. Compared to other groups, the receptor down-regulation was the most prominent in 15-day paracetamol administered group. In contrast, the receptor density became greater in the rats receiving paracetamol for 30 days. If analgesic efficacy is seemed to depend on 5-HT_{2A} receptors regulation, the reverse of such down-regulation observed in 30-day treated group would result in the reduction of analgesic efficacy demonstrated by the tail flick test. It has been accepted that prolonged reductions of pain sensation by any processes including chronic analgesic consumption often lead to functional changes to restore sensitivity. The phenomenon of analgesic rebound headache (Kudrow, 1982) may represent a situation where such a compensatory mechanism plays a major role in perpetuation of pain. An up-regulation of 5-HT_{2A} receptors has been reported in migraine patients with analgesics rebound

headache (Srikiatkhachorn et al., 1994). Since this subtype of 5-HT receptor involves in pain facilitation, an increase in receptor numbers observed in these patients may result in a hyperalgesic state and the development of chronic daily headache.

In contrast to the decrease in 5-HT_{2A} receptor number, paracetamol induced the up-regulation of 5-HT uptake sites or [^{3}H]imipramine binding sites (IBS) in 15-day treated groups. The density of 5-HT uptake sites became lesser in the rats receiving paracetamol for 30 days when compared with 15-day treated groups. Based on the fact that the density of 5-HT uptake sites tend to parallel the levels of 5-HT (Palkovits et al., 1981), therefore, the increase of 5-HT as shown in platelets, may induce the increasing of the number of 5-HT uptake sites in 15-day paracetamol administration. Moreover, the reverse of such up-regulation may relate to the reduction of the levels of 5-HT in platelets observed in 30-day treated group.

If one assume that paracetamol can induce 5-HT release, chronic use of this drug may deplete 5-HT from its storage sites. Consequently 5-HT depletion for longer period may up-regulate the 5-HT_{2A} receptors. This hypothesis corresponds to the previous finding of an increase in 5-HT receptor numbers in rat cortical and pontine membrane after being chronically treated with pyrazole derivative, phenazone (Pini et al., 1994).

In 15-day paracetamol treatment, we found that paracetamol evoked a significant increase of 5-HT levels without significant alteration in 5-HIAA levels in platelets. These findings are of interest in 30-day paracetamol treated groups, almost no change in the concentration of 5-HT was observed whereas a significant elevation in platelet 5-HIAA levels were found evidenced.. It is possible that paracetamol may

increase the turnover rate of 5-HT and this process possibly associates with the elevation of analgesic activity. This assumption is supported by the observation of Bensemana and Gascon (1978) and Groppetti et al. (1988) that there was a correlation between analgesia induced by paracetamol and the increase in the turnover rate of 5-HT in the brain stem of rat. In particular, Groppetti et al. (1988) demonstrated that ASA increased the 5-HIAA concentration in several areas of rat brain. Mechanism underlying this process is still obscure, but the increased of tryptophan hydroxylase activity, the rate limiting enzyme of 5-HT synthesis, may play a role in this respect. The elevation of this enzyme activity results in the increase of 5-HT synthesis. The following consequence is the increase of 5-HT concentration as observed in 15-day paracetamol treated groups in our experiment. An increase of monoamine oxidase activity, one of the primary enzymes involved in the catabolic inactivation of monoamine neurotransmitters is another possible explanation.

The role played by 5-HT in the control of food intake and energy expenditure has generated a great deal of interest in the recent years. An accumulating data suggest that the 5-HT system indeed represents a key part of the neural network involved in the regulation of food intake and energy balance (Roth, 1994; Blundell, 1992; Blundell et al., 1995). Recent studies by Wilckens and co-workers (1992) as well as by Bovetto and Richards (1995) on the functional assessment of various serotonin receptor subtypes on food intake and metabolic rate in rats have emphasized the involvement of 5-HT_{1B} and 5-HT_2 receptors in the control of food intake and that of 5-HT_{1A}, 5-HT_{1B} and 5-HT_2 receptors in the control of energy expenditure. In the present study, we found that chronic administration of paracetamol caused the loss of

body weight. This effect may be related to the changes of 5-HT_2 receptors observed in this group of study.

ACUTE EFFECT OF PARACETAMOL

The data reported in this study demonstrated that acute treatment with paracetamol is able to decrease the number of 5-HT_{2A} receptors and increase the number of 5-HT uptake sites in the membrane of frontal cortex of rat brain in the same manner as previous study that found in 15-day paracetamol-treated group. However, the effect of acute treatment with paracetamol are lesser than those of 15-day paracetamol treated-group. Moreover, the reduction in the number of 5-HT_{2A} receptors occured concomitantly with the elevation of pain threshold as measured by the tail flick test. The acute effect of paracetamol on 5-HT_{2A} receptors reported herein is corresponded with an observation of Pini et al. (1996).

Darmani and co-workers showed that, after agonist exposure, the ability of 5-HT_2 receptors system to induce down-regulation appears in a relatively short period of time (Darmani et al., 1992). Additionally, it has been shown that acute administration of paracetamol can increase the level of 5-HT in cerebral cortex and pons (Pini et al., 1996, 1997). From these observations, one can suggest that acute administration of paracetamol may lead to the changing in central 5-HT neurotransmission, possibly by accelerating the rate of release and/or the rate of 5-HT synthesis. The increase in 5-HT availability in the 5-HT synaptic transmission results in the adaptation of the 5-HT_{2A} receptors. The decreased number of 5-HT_{2A} receptors including the increased number of 5-HT uptake sites can be viewed as the compensatory adjustment to an increasing in serotonergic neuronal activity.

In addition, we also found that paracetamol at a dose of 400 mg/kg produced a significant elevation of pain threshold compared to the vehicle treated group as measured by the tail flick test. The present data is consistent with results obtained by Hunskaar et al. (1986) and Pini et al. (1996) by using the hot plate test. The data reported in this study, when correlated with the previous studies suggest that the decrease in the density of 5-HT_{2A} receptors lasts only few hours in rats receiving only one dose of paracetamol is also involved in the elevation of pain threshold. The down-regulation of 5-HT_{2A} receptors can be the consequence of the increased 5-HT levels.

Our results agree with the previous reports indicating that antinociceptive effect of acetylsalicylic acid in the hot plate test is associated with an increased brain 5-HT content and a decrease in the number of serotonin receptors in rat cortical brain membranes, by using [^{3}H]5-HT as a ligand (Pini et al., 1994). Furthermore, Sandrini et al. (1993) investigated the acute effects of phenazone on brain 5-HT binding sites, and found that phenazone produced a significant decrease in [^{3}H]5-HT binding sites both in pons and cerebral cortex and produced a significant elevation in response latency in hot plate test. Accordingly, Sandrini and coworkers (1993) concluded that their results were consistent with the hypothesis that, in part, the analgesic effect of phanazone may be attributable to a drug-induced release of central 5-HT.

In conclusion, these results provide further evidence for a central 5-HT dependent antinociceptive effect of paracetamol. Our study suggests that the elevation of serotonergic concentrations may significantly induce the down-regulation of 5-HT_{2A} receptors and up-regulation of 5-HT uptake sites in acute and 15-day paracetamol administration. Down-regulation of 5-HT_{2A} receptors in response to 5-

HT release may be a major step in mechanism underlying analgesia produced by this agent. On the contrary, chronic use of paracetamol for 30 days may result in 5-HT depletion. Consequently, the 5-HT depletion may produce the compensatory effects by re-adaptation of the 5-HT_{2A} receptors at post-synaptic membrane and 5-HT uptake sites at the pre-synaptic membrane. Since paracetamol does not interact directly with 5-HT_{2A} receptors, we can suppose that paracetamol is able to increase 5-HT levels either by modifying 5-HT reuptake, 5-HT release and turnover rate or by acting on the neurotransmitter metabolism (Fig. 85 and 86).

Proposed Mechanism of Paracetamol

Chronic Effect

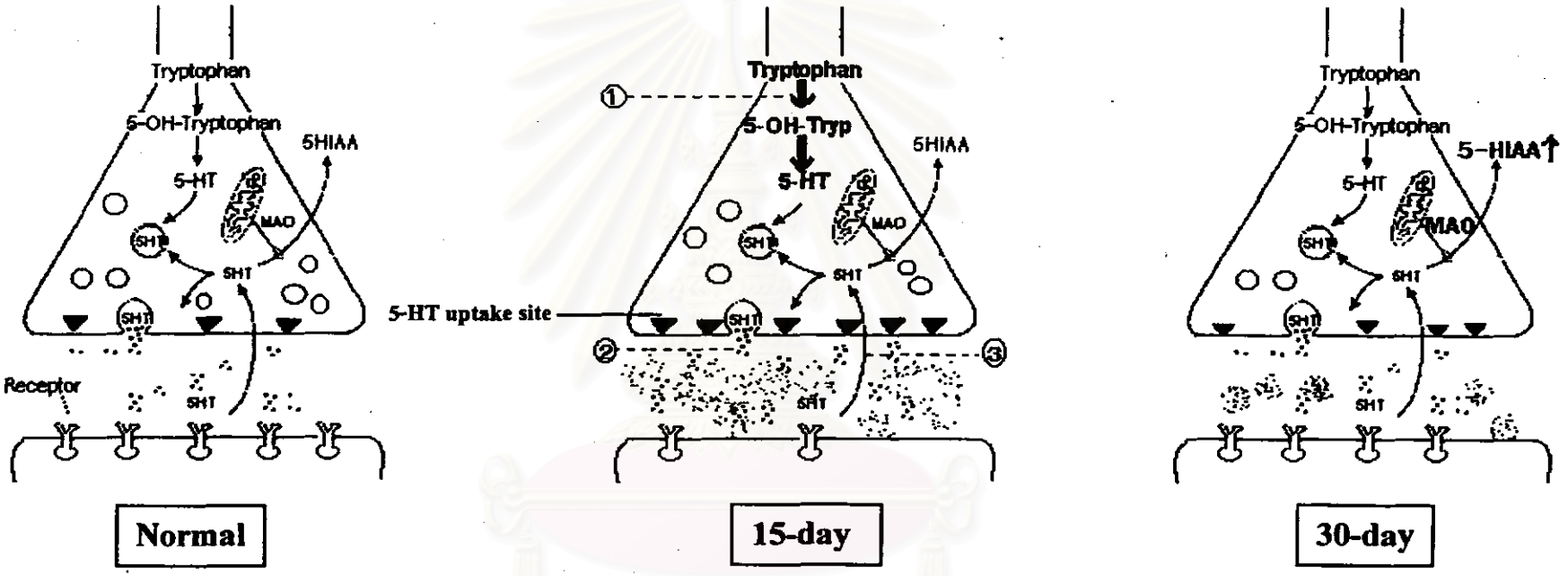

Figure 85. Possibles sites where paracetamol act on central serotonin neurons in 15 and 30 day treatment

1. Enzymatic synthesis. Tryptophan, the precursor of serotonin, is converted to 5-hydroxytryptophan (5-OH-tryptophan) by tryptophan hydroxylase. Paracetamol may interfere the activity of the enzyme.
2. Release. Paracetamol may interfere with the rate of release of 5-HT and thus changing of 5-HT level.
3. Reuptake. Paracetamol may modify the uptake mechanism and thus increase or decrease the efficiency of transmission.

Proposed Mechanism of Paracetamol

Acute Effect

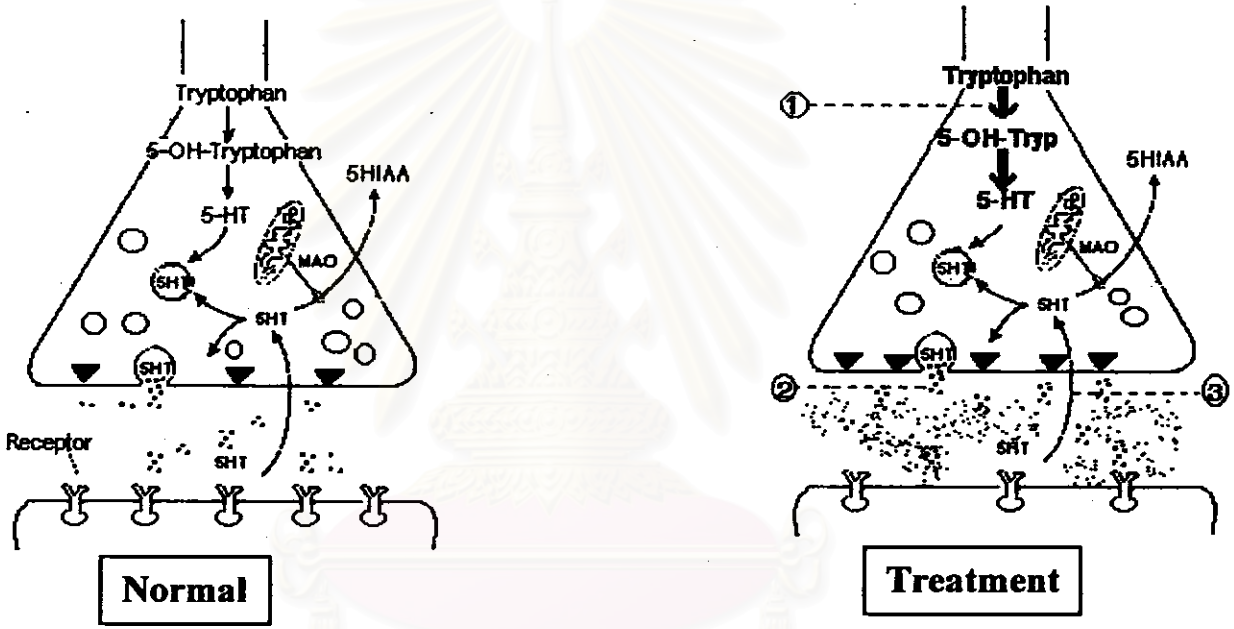

Figure 86. Possibles sites where paracetamol act on central serotonin neurons in acute treatment

1. Enzymatic synthesis. Tryptophan, the precursor of serotonin, is converted to 5-hydroxytryptophan (5-OH-tryptophan) by tryptophan hydroxylase. Paracetamol may increase the activity of the enzyme.
2. Release. Paracetamol may accelerate the rate of release of 5-HT and thus increasing of 5-HT level.
3. Reuptake. Paracetamol may decrease the uptake mechanism.