CHAPTER II

LITERATURE REVIEWS

A. Stress

Stress is defined as a state of threatened homeostasis. When faced with the stressors, the body responds to stress by changing of physiological and psychological systems. Stressors can be divided into 2 main categories, physical and psychological stressors. Physical stressors that have either a negative or disturb body function such as cold or heat exposure, noise exposure, hypoglycemia, chemical (i.e. all poisons), pain elicited from many different chemical and physical agents and many others. Psychological stressors affect emotional processes and many result in behavioral changes such as anxiety, fear, social isolation or frustration. Many of the stressors above and used in animal research; however, are mixed and act in concert, such as handling, anticipation of painful stimulus and immobilization stress.

In term of duration, stressors may be divided into acute stressors that single or intermittent exposure to stress, and chronic stressors that prolonged or continuous exposure to stress. It should be noted that many stressors differ in their intensity.

Stress response is known as general adaptation syndrome (GAS) which is composed of three stages; alarm reaction, resistance and exhaustion. Alarm reaction is immediate responses to internal and external stressors such as increase of heart rate or fight or flight behavior, respectively. These responses are predominantly regulated by sympathetic nervous system (Gilbey and Spyer, 1993). The body releases epinephrine and a variety of other psychological mechanisms to combat the stress and to stay in control. Once the stressor is removed, the body will go back to normal. If the cause for the stress is not removed, GAS goes to its second stage called resistance or adaptation. At this stage, corticosteroid is released and acts on varieties of target cell in order to adjust homeostasis. This response is so called resistance stage because the living things are able to resist the stressors for weeks to a few months. However, prolonged stress more than a few months leads to breakdown of homeostasis due to depletion of

physical and psychological resources and exhaustion (Pacak and Palkovits, 2001). Therefore, the third stage of GAS is called exhaustion which the body has run out of its reserve of body energy and immunity. Mental, physical and emotional resources suffer heavily. Stress response tends to protect the organism from the immediate health threat of the stressor but in the long-term these same effects can be dangerous to the body. The body experiences "adrenal exhaustion". The blood sugar levels decrease as the adrenals become depleted, leading to decreased stress tolerance, progressive mental and physical exhaustion and illness such as osteoporosis, atherosclerosis, hypertension, diabetes mellitus. In addition to physical illness, other conditions may be associated with prolonged activation of the stress system, including depression, anorexia nervosa, obsessive compulsive disorder, panic anxiety, chronic active alcoholism, alcohol and narcotic withdrawal, excessive exercising.

1. The stress system

The principle components of the adaptive response to stress are the hypothalamic-pituitary-adrenal axis (HPA axis) and the central sympathetic system (locus coeruleus-norepinephine (LC/NE)-autonomic systems) and their peripheral mediators, epinephrine (E), norepinephrine (NE) and cortisol. Activation of the stress system leads to behavioral and peripheral changes that improve the ability of the organism to adjust homeostasis and increase its chances for survival, utilizing inputs from many areas in the brain and periphery in contributing to the modulation of the intensity and duration of the stress response. In addition, the stress system also includes other brain are involved in important functions such as the analysis and retrieval of information, the appraisal process, the setting of emotional tone, the evaluation of coping strategies and the implementation of appropriate adaptive response (Chrousos and Gold, 1992).

1.1 The HPA axis

During stress, corticotrophin releasing hormone (CRH) released from the paraventricular nucleus of hypothalamus drives adrenocorticotropin releasing hormone (ACTH) secretion from anterior pituitary which stimulates cortisol secretion.

Glucocorticoids are the final effectors of the HPA axis and participate in the control of whole body homeostasis and the organism's response to stress. They play a key regulatory role on the basal activity of the HPA axis and on the termination of the stress response by acting at extra hypothalamic centers, the hypothamus and the pituitary gland. The inhibitory glucocorticoids feedback on the ACTH secretory response acts to limit the duration of the total tissue exposure to glucocorticoids. Acute glucocorticoids secretion during stress serves several roles, including enhancement of cardiovascular function and mobilization of fuel. Cortisol also significantly contributes to the inhibition on the growth hormone and gonadal axis, as well as to feedback restraint upon an activated immune system. Chronic cortisol excess is almost always deleterious and includes excessive fear, insulin resistance/visceral fat deposition and chronic suppression of the mesocorticolimbic dopamine reward system (Chrousos, 1992).

1.2 The LC/NE-autonomic system

The LC/NE system resides in the mid-pons and contains the highest concentration of noradrenergic cell bodies that projects to the cerebral cortex, the amygdala, the hippocampus and the PVN of the hypothalamus (Gold and Chrousos, 2002). Acute activation of this system leads to release of norepinephrine from an extensive network of neurons throughout the brain, producing an enhanced state of arousal, which is critical for adaptive response to stress. Prolonged activation leads to compensatory increases in the biosynthesis of norepinephrine and consequently, to a sustained increase in norepinephrine releases such that brain norepinephrine contents does not decline and may even increase. In response to chronic stress, the activity of the LC/NE system is affected by environmental cues, such as the availability of effective coping response. For example, exposure to inescapable or uncontrollable stress may lead to dysfunction of the LC/NE system, and consequently, to depress norepinephrine release, which was associated with learned helplessness situation (Petty et al., 1993).

The stress system (the HPA axis and the LC/NE system) also interacts with other central nervous systems that influence the retrievability and analysis of information, the initiation of specific action and the setting of the emotional tone.

2. Stress response system

2.1 The mesocorticolimbic dopamine system

Dopamine has been implicated in the stress-related regulation of HPA axis. There is evidence that central dopaminergic systems exert a positive control on the HPA axis and the LC/NE system (Sullivan and Dufresne, 2006; Tsigos and Chrousos, 2002). In addition, the mesocortical and mesolimbic dopamine system are activated by the HPA axis and the LC/NE system during stress (De La Garza and Mahoney, 2004). Mesocortical dopamine system innervates the prefrontal cortex, which is involved in anticipatory phenomena and cognitive function (Nestler et al., 2001). Mesolimbic dopamine system is linked to the nucleus accumbens and is thought to play a role in motivation and reward phenomena (Nestler et al., 2001). This system is believed to be involved in the activation of goal-directed behavior and its inhibition may lead to emotional indifference and lack of initiation. This system has been shown to be highly sensitive to stress (Puglisi-Allegra and Cabib, 1990). It was suggested that stressful experiences alter dopamine (DA) metabolism and release in this area. Moreover, repeated exposure to stress may lead to different responsiveness to subsequent stressful experiences depending on the stressor, leading to different changes on mesolimbic function. Exposure to a single unavoidable/uncontrollable aversive experience may lead to inhibition of DA releases in the NAc as well as to impair response to both rewarding and aversive stimuli (Cabib and Puglisi-Allegra, 1996a, b). The effects of stressful experiences on DA functioning in the mesolimbic system can be very different or even opposite depending on the controllability of the situation, and its life history (Cabib and Puglisi-Allegra, 1996a, b).

2.2 The amygdala/ hippocampus

Amygdala/ hippocampus complex is activated during stress, primarily by noradrenergic neurons and is important for retrieval and emotional analysis of information pertinent to the stressor. The amygdala receives more basic sensory information through thalamo-amygdala pathways, more elaborated information through thalamo-cortico-amygdala pathways and even more complex information, concerning

the general context, from the hippocampus (LeDoux, 1996). In addition, the hippocampus and related cortical areas are implicated in the processes of formation and retrieval of explicit memories, from cortical and subcortical storages. Input from these areas to the amygdala, playing as internal stressors, may lead to stress responses triggered by such memories, even in the absence of any external event. Hence, the amygdala is essentially involved in the analysis of the emotional significance of external stressors, either as individual stimuli or as complex situations, as well as the emotional appraisal of internal stressors (LeDouX, 1992; Rogan and LeDouX, 1996). Different outputs from the central nucleus of the amygdala regulate the expression of different behavioral, autonomic and neuroendocrine responses (Davis et al., 1994); projections to the lateral hypothalamus mediated the activation of the sympathetic component of the autonomic nervous system, projections to the LC/NE system and ventral tegmental area (VTA) are involved in the activation of the noradrenergic and dopaminergic system, and very importantly, direct projections to the PVN of the hypothalamus, or indirect projections by way of the bed-nucleus of the stria terminalis (BNST) mediate the activation of the characteristic neuroendocrine responses to stress.

It has been shown that exposure to stressors causes an array of biochemical, physiological and behavioral changes that enable the individual to cope with new situation (Di Chiara and Tanda, 1997; Di Chiara et al., 1999; Pecoraro et al., 2004). The neurochemical changed that occur in discrete brain regions following exposure to stress (Di Chiara et al., 1999; Sunanda et al., 2000). The serotonergic and dopaminergic pathways innervating the striatum, hippocampus, frontal cortex and amygdala are altered by exposure to stress (De La Garza and Mahoney, 2004). Brain dopamine concentrations have been reported as unchanged, while dopamine turnover was increased, unchanged or decreased. In the prefrontal cortex and nucleus accumbens, the dopamine levels was increases when exposure to acute stress (De La Garza and Mahoney, 2004), where as chronic exposure to stress decreased dopamine levels (Di Chiara et al., 1999; Sunanda et al., 2000). Moreover, decrease in GABA concentration, uptake and activity of glutamate decarboxylase was observed in striatum and frontal cortex following acute and chronic cold stress (Otero Losada, 1988; Bowers et al.,

1998). All these changes in neurotransmitter are believed to result in behavioral changes including feeding behavior. However, stress and diet associations are particularly complex. Some studies have found that stress alters the hedonic response to pleasurable stimuli, a behavioral change similar to that seen in patients suffering from drug abuse. For example, chronic stress (speech test or restraint stress) increase intake of a preferred food such as cake or chocolate biscuits (Oliver et al., 2000). In contrast, Gamaro et al. (2003) reported that sucrose consumption was decreased in rats exposed to chronic stress paradigm in which a different mild stressor was applied each day. Therefore, different types and degrees of stressors can have opposing effects on the consumption of food and test solution.

B. Reward system

1. Neuroanatomy of reward system

The anatomical structures of the reward pathway have complex interrelationships, and are modulated by other parts of the brain and other neurochemical. The brain reward pathway is located in the limbic system. The function of the limbic system is to monitor internal homeostasis, mediate memory, mediate learning and experience emotion. It also drives important aspects of sexual behavior, motivation and feeding behavior. The parts of the limbic system include the hypothalamus, amygdala, hippocampus, septal nuclei and anterior cingulate gyrus. An important in the function of the limbic system is implicated in various reward-modulated behaviors, including food reward via the mesolimbic dopamine pathway, which is composed of dopaminergic neurons with cell bodies in the ventral tegmental area (VTA) that project to the nucleus accumbens (NAc), the prefrontal cortex, the hippocampus and the amygdale (Figure 2-1). The primary neurotransmitter of the reward pathway is dopamine. Various rewards such as food intake or drug of abuse share a common action in that they increase dopamine levels in the brain reward system. In addition to dopamaine, other neurotransmitters such as serotonin, GABA, as well as endogenous opiates also modulate dopamine levels in the brain reward pathway.

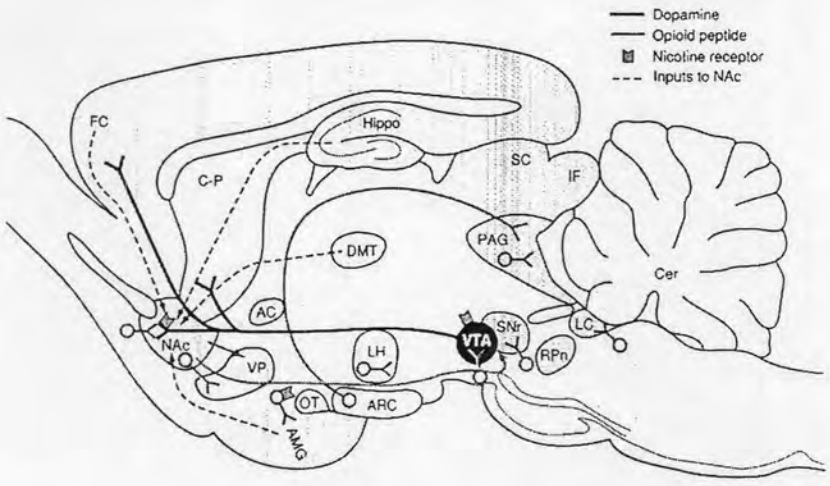

Figure 2-1 Schematic drawing depicts the location of the reward system in a sagittal section of the rat central nervous system. VTA, ventral tegmental area; NAc, nucleus accumbens; AMG, amygdala; FC, frontal cortex; Hippo, hippocampus; LH, lateral hypothalamus (Nestler et al., 2001)

2. Neurotransmitter of reward system

Dopamine (DA) is a main neurotransmitter of reward pathway. It is a one of catecholamine group because the structure is with a cathechol nucleus and an ethylamine group attached at its 1 position. Dopamine is found in peripheral and central nervous system. It cannot cross the blood-brain barrier, must be produced within brain. The synthesis pathway of DA is shown in Figure 2-2. The initial step in the synthesis of DA is the facilitated transport of the amino acid L-tyrosine from blood into brain. Dopaminergic neurons contain the enzyme tyrosine hydroxylase (TH), the rate limiting enzyme, which convert tyrosine to dihydroyphenylamine (DOPA). Thereafter, L-aromatic amino acid decarboxylase (AADC) converts DOPA to DA. Released DA is converted to dihydroxyphenylacetic acid (DOPAC) by intraneuronal monoamine oxidase (MAO) after reuptake by the nerve terminal. Released DA is also converted to homovanillic acid (HVA), at an extraneuronal site, through the sequential action of catechol-*O*-methyltransferase (COMT) and MAO (Kuhar et al., 1999).

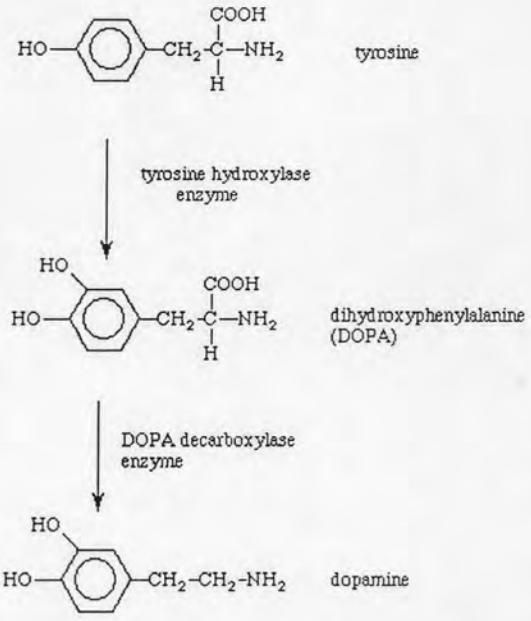

Figure 2-2 Diagram depicts the biosynthesis pathway for dopamine (Kuhar et al., 1999)

3. Neuroanatomy of food reward pathway

Research has shown that eating activates neural substrates in a similar manner to drugs abuses, although with important differences of degree. When we start eating our favorite food, the perception of food reward generate by oral taste bud cells, convey taste messages by afferent sensory fibers (i.e. branches of the facial (chorda tympani and greater superficial petrosal), glossopharyngeal, and vagus (superior laryngeal nerves) to the rostral part of the nucleus of the tractus solitarius (NTS). The ascending tastes from the NTS is conveyed to parabrachial nucleus (PBN) of the pons, ventral tegmental area (VTA), nucleus accumbens (NAc), striatum, thalamus and cerebral cortex, which collective sense and discriminate among different tastes and textures, assigning reward value to them. Reward valuation involves the release of dopamine from neurons that originate in the VTA and project to NAc, striatum and other brain areas (Kelley and Berridge, 2002; Kelley et al., 2005). Acting in these forebrain areas, dopamine potently augments the drive to obtain a rewarding stimulus, but it is not directly responsible for the hedonic experience itself. Rather, μ-opioid receptor signaling in the NAc and adjacent forebrain structure (activate in part by dopamine

release) is implicate in the hedonic experience (Kelley and Berridge, 2002; Kelley et al., 2005), although wanting and liking ordinarily occur together.

One mechanism whereby activation of the VTA to NAc pathway may promote consumption of palatable food involves projections to the lateral hypothalamic area. This brain area contains neurons that potently stimulate food intake and is supplied by fibers not only from striatum and orbitofrontal cortex, but also from the arcuate nucleus (ARC) and other crucial hypothalamic areas for energy homeostasis. Food-intake-stimulatory neurons in the hypothalamus area seem to be constrained by tonic inhibition that can be relieved by activation of reward pathway, thereby engaging motor programs that stimulate feeding behavior (Kelley et al., 2005). Lateral hypothalamic area neurons supplying the NTS, may attenuate the response to satiety signals, increasing the amount of food consumed during a meal. These considerations support a view of the lateral hypothalamic area as an integrative node for homeostatic, satiety and reward-related inputs that collectively govern motor programs that activate feeding behavior.

4. Normal control of food intake

The regulation of food intake is a complex process. As the center regulation of food intake is hypothalamus, it consists of the feeding center, the lateral hypothalamus and the satiety center, the ventromedial hypothalamus (Kupferman et al., 2000). The hypothalamus receives signals from many sources such as sensory in put from vagus nerve or chemical signals from the gastrointestinal tract; e.g. gherlin and cholecystokinin (CCK) or receives from adipose tissue, e.g. leptin, etc (Small and Bloom, 2004). These signals may lead to stimulate or inhibits food intake depend on type of chemicals such as gherlin potently stimulate food intake (Wren et al., 2001), whereas leptin inhibit food intake (Friedman and Halaas, 1998). Additionally, other hypothalamic nuclei are involved in control of food intake such as, the arcuate nucleus of the hypothalamus consist of two neuronal populations: the antagonistic orexigenic neuropeptide Y (NPY) and anorexigenic POMC neurons, that project to the paraventricular nucleus (PVN) and other brain areas involved in the modulation of food intake including the bed nucleus of

the stria terminals (BST), the medial preoptic area (MPO), the amygdala, etc (Broberger and Hökfelt, 2001; DeFalco et al., 2001). Moreover, the arcuate nucleus also project to melanin-concentrating hormone-producing neurons in the lateral hypothalamus (MCH) provides an indirect pathway to the cerebral cortex for metabolic signals (Broberger and Hökfelt, 2001). The cortex in turn projects back to the lateral hypothalamus and (Broberger and Hökfelt, 2001). Further, the lateral hypothalamus also receives an inhibitory input from the shell of nucleus accumbens, which in turn is regulate through excitatory inputs from the prefrontal cortex (Maldonado-Irizarry et al., 1995; Saper et al., 2002). Therefore, the lateral hypothalamus is positioned to integrate both homeostatic and reward-related signals in the gating of food intake.

C. Biology of opioids

1. Opioid ligands and receptors

Endogenous opioids and their receptors are found to localize in central, peripheral and autonomic nervous system (Akil et al., 1984; Holaday, 1983; Olson et al., 1996; Yamada and Nabeshima, 1995). They play an important role in modulating endocrine, cardiovascular, gastrointestinal and immune system (Vacarino and Kastin, 2000). Moreover, the endogenous opioids widely distribution in the brain suggests that they serve general role as neurotransmitters or neuromodulators. The endogenous opioids have been divided into three families; the enkephalin, dynorphin and endorphin. There is a different precursor protein for each of the major types of opioid peptides. Proopiomelanocortin (POMC) is the precursor for β-endorphiin, prodynorphin is the precursor for dynorphin while proenkephalin A is the precursor for Met- and Leu-enkephalin.

1.1 The β –endorphin

β–endorphin is present in the nucleus arcuatus of the mediobasal hypothalamus and the nucleus tractus solitarius (NTS) of the caudal medulla. An extensive fiber system originating in the arcuate nucleus terminates in many areas of

the brain which have been implicated in the stress response. In addition, some of these structures might also be innervated by POMC neurons located in the NTS which project laterally and ventrally and which also enter the spinal cord. Endocrine cells of both the anterior and the intermediate lobe of the pituitary, cells of some peripheral tissues and immunocytes also contain, synthesize and release POMC peptides.

1.2 The dynorphin

Prodynorphin neurons are widely distributed in brain areas associated with stress. Prodynorphin and related peptides are present in the magnocellular neurons of the paraventricular nucleus (PVN) of the hypothalamus. In addition, these peptides are found in the NTS, an area classically associated with the regulation of vagal and other autonomic functions. Further, prodynorphin neurons occur in the limbic system and in areas of the spinal cord involved in transmission of nociceptive stimuli.

1.3 The enkephalin

Proenkephalin neurons have a wide distribution throughout the central and peripheral nervous systems. They are localized predominantly in interneurons, some of which form local circuits, and others, longer tract projections. Proenkephalin neurons are abundant in the PVN and the nucleus arcuatus of the hypothalamus. A number of proenkephalin neurons exist in limbic system structure, e.g., the hippocampus, the septum and the bed nucleus of the stria terminalis. Septal proenkephalin neurons project directly to the amygdala.

2. Opioid receptors

Pharmacological studies have defined at least three classes of opioid receptors, termed μ, δ and κ (Reisine, 1995; Snyder and Pasternak, 2003). These opioid receptors differ in their affinity for binding with various opioid ligands. Endorphin, enkephalin and dynorphin, bind selectively to μ-, δ - and κ –receptor, respectively (Reisine and Bell, 1993). In general, the opioid receptors belong to the G protein-coupled receptor superfamily and link to the G_i/G_o family of G protein. The μ- and δ -receptors coupled through G_i/G_o-proteins to activate an inwardly rectifying

potassium conductance and to inhibit voltage operated calcium conductance whereas κ-receptor only inhibit voltage-operated calcium conductance (Williams et al., 2001). However, in some cell types, κ-receptor also coupled to activation of an inwardly rectifying potassium conductance. Therefore, the opioid receptors will share common effectors mechanisms in inhibitory signaling pathway. However, some pharmacological and biochemical data suggest that addition subtypes may be generated and that heterodimers may form between μ and δ receptors (Gupta et al., 2006).

Recently, the behavioral effects mediated by opioids differ depending on the opioid receptor type with which they interact. The μ-receptor mediates most of the opioid actions, including analgesia, tolerance and reward (Williams et al., 2001). The function of the central δ -receptor is less well understood, but the κ -receptor has been receiving much research interest because many studies suggest that activation of the κ -receptor opposes a variety of μ-receptor mediated actions throughout the brain and in the spinal cord. For example, systemically applied μ-receptor agonist function as positive reinforces and increase locomotor activity (Del Rosario Capriles and Cancela, 2002). In contrast, κ -receptor agonists have aversive and sedating effects (Del Rosario Capriles and Cancela, 2002).

3. The interaction of opioids and food reward

There was evidence shown that opioid modulate the mesolimbic dopamine system by inhibiting GABA neurons in the ventral tegmental area (VTA) (Bergevin et al., 2002; Devine et al., 1993; Kelly and Berridge, 2002). GABA neurons basically inhibit dopaminergic neuron in the VTA causing the inhibition of function of the dopaminergic neuron of NAc (Bergevin et al., 2002; Devine et al., 1993). Thus when opioids inhibit GABA neurons, dopaminergic neurons are free to fire more often. In essence, opioids remove the brakes from dopaminergic neuron and allow them to fire more rapidly resulting in an increase of dopamine release (Kelley et al., 2002; Koop, 1997; MacDonald et al., 2004). In deed, populations of μ-, δ- and κ-opioid receptors have been identified on mesolimbic dopamine neurons (Mansour et al., 1987). In common, μ- and δ -receptor agonist increase extracellular dopamine levels in the nucleus accumbens (Spanagel et al., 1992). The effects of both μ- and δ -receptor agonist

(DAGO, [D-Ala^2, *N*-methyl-Ple^4, Gly^5-ol] enkephalin] and DSLET) on dopamine overflow was result from the activation of their respective receptor in the ventral tegmental area (Spanagel et al., 1992; Devine et al., 1993), which were increase dopamine levels. In contrast, activation of κ-receptor agonist, U69593, given into the nucleus accumbens decrease dopamine levels in the nucleus accumbens (Spanagel et al., 1992). The involved receptors are thought to be located in the ventral tegmental area (for μ-opioid receptors) and the nucleus accumbens (for μ- δ- and κ-opioid receptors).

Since opioids are also well-known hedonic agents, their actions in brain reward systems are deserved to be investigated with regard to food intake. Many studies have suggested that food rewards and drug rewards may share some common neural substrates, including substantial evidence that opioid receptors play key roles in both feeding and reward (Kelley et al., 2002). For example, opioid receptor antagonist such as naloxone block the effects of agouti relate protein (AgRP) to increase feeding (Hagan et al., 2001). Recently, Hayward and colleagues (2002) reported that mice lacking either enkephalin or β-endorphin peptide showed a deficit in the ability of food reward to increase bar pressing behavior. Moreover, there evidence indicate that opioids are thought to prolong intake, particularly of highly palatable foods, but not initiate intake (Glass et al., 1999; Hanlon et al., 2004; Zhang et al., 2003). Studies of opioid receptor function on food reward by opioid antagonists have been shown to inhibit intake of highly preferred foods than less preferred foods. This evidence strengthens the argument that opioid and their receptors are involved in the response to the quality of the food, rather than to hunger (Glass et al., 1999; Pellegrini et al., 2005).

As the previous review of food reward mechanism, the nucleus accumbens and its dopaminergic inputs have been implicated in food reward. Administration of opioid receptor agonist in to the VTA, the originally of dopaminergic system, contribute dopamine in the nucleus accumbens release, which appears to increased sucrose consumption (Hajnal and Norgren, 2001; Macdonald et al., 2003, 2004). On the other hand, an opioid receptor antagonist (naloxone) infused directly into the nucleus accumbens decreases fat intake in hungry rats (Zhang et al., 1998). In addition, stimulation of μ-opioid receptor in the nucleus accumbens increases the break point for food reinforcement in a progressive ratio task (Zhang et al., 2003).

Therefore, opioids are thought to predominantly involve in the modulation of food reward by regulated the mesolimbic dopamine system via opioid receptors.

4. Modulatory effects of stress on opioid system

Some stressors (such as forced swimming, foot shock or restraint stress) are known to activate endogenous opioid systems whereas other does not. Previous research suggested that the activation of opioid or nonopioid systems depends on the duration of stress exposure, as daily exposure to 6-h of forced walking in mice for 6 or 9 days produced naloxone sensitive analgesia, whereas a single 6-h exposure to the walking stress produced non-opioid analgesia that was naloxone-insensitive. Moreover, animals lacking of β-endorphin shown absent of stress-induced analgesia after exposure to stress (Rubinstein et al., 1996) , as well as δ-opioid receptor have been associated with stress response behavior, because δ- agonists reduced the immobility of rats in a forced swimming stress (Broom et al., 2002). In contrast, stress-induced analgesia was blocked by nor-binaltorphimine (nor-BNI), κ-opioid antagonist (McLaughin et al., 2003).

Exposure to acute or chronic stress has different effect to opioid system. Acute stress produces immediate analgesia in several pain tests such as animal exposure to 1 h restraint stress shown an increased latency in the tail-flick test (Gamaro et al., 1998). This response was mediated by the endogenous opioid peptide because opioid receptor antagonist can reverse this effect of acute stress (Mogil et al., 1996). Therefore, it is possible that the phenomena of adaptation to chronic stress modulated by several hormones, especially corticosteroid, may result in up-or down-regulation of opioid receptor in different brain structure that related to food preferences.