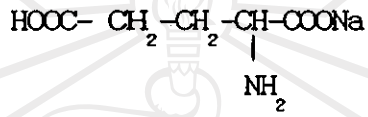
LITERATURE REVIEW

Monosodium glutamate (MSG) is widely used as food additive. It is a sodium salt of naturally occurring amino acid, glutamic acid. MSG has the following structure:



The mechanism that causes the increase in flavour sensation is not clearly established. One theory is that MSG increases the sensitivity of certain taste buds. It may be effective by stimulating greater saliva flow or by acting to combine with trace metals present, thus freeing more taste bud receptors to react to the taste-stimulating compounds present (Pryde, 1973).

Although glutamate is found in all proteins in the body, an excess amount can become toxic and destroy nerve cells in infant mice (Olney, 1970). Therefore, MSG is probably not a wholly innocuous substance. It was proposed as the cause of the Chinese Restaurant Syndrome (Schaumburg, et al., 1969). Many symptoms have been suggested as component of the syndrome. Schaumburg, et al. (1969) reported that three categories of symptoms could be elicited after intravenous injection of 125 mg of MSG. The first symptom was a burning sensation, usually beginning over the chest and spreading to the neck, shoulders, forearms and abdomen. The second category of symptoms was facial

pressure, a sensation of tightness and pressure over the molar area, occasionally extending into the zygomatic and retroorbital region. The third type of symptom was chest pressure, a sensation of pressure over the substernal area, occasionally radiating to the axillae or neck. Headache was a consistent complaint. Moreover, they found that oral administration of MSG also caused symptoms and an increase in intensity of response with increase in dosage.

Experimentally, Lucus and Newhouse (1957) reported that administration of sodium L-glutamate to suckling mice caused degeneration of the ganglion-cell layer and failure of formation of the inner nuclear layer of the retina, leaving only the receptor cell intact. In 1960, Potts, et al. agreed with the report of Lucus and Newhouse (1957) in the effect of MSG on the formation of the inner nuclear layer and they also found the abnormal electroretinogram (ERG), an ERG consisting of a negative a-wave only, in animal receiving glutamate.

In newborn mice, only a single subcutaneous injection of MSG (dosage varied from 0.5 to 4 mg/gm of body weight) induced brain lesions characterized by intracellular edema and neuronal necrosis developed within a few hour of treatment at every dose tested. Certain structures located in a paramedian plane and bordering the floor of the third-ventricle were perferentially affected. At the base of the brain, preoptic and arcuate nuclei of the hypothalamus were selectively destroyed along with scattered neurons within the median eminence (Olney, 1969). Light microscopic study and histofluorescence technique revealed a pronounced morphological alteration in hypothalamus. The

number of perikarya in the arcuate nucleus decreased approximately 60-80% in mice treated postnatally with MSG 2.5 mg/gm body weight for 5 days (Holzwarth-Mc Bride, et al., 1976). Tanaka, et al. (1978) reported that by injection into suckling mice MSG induced hypothalamic lesions localized mainly in the preoptic region and a region surrounding the median eminence, the arcuate nucleus was the site of the most affected part. The severity and extent of the lesions varied according to the age of the animals when treated. It was most prominent in the youngest mice.

In the primate, Olney and Sharpe (1969) studied in baby rhesus monkey (seperated from its mother 8 hours after birth) by injection of MSG, 2.7 gm/kg body weight. Three hours after treatment, a lesion affecting the periventricular-arcuate region of the hypothalamus was apparent under light microscope and an electron microscopic examination showed a massive dilated dendritic process and degenerating neuron.

In rats, which have been studied extensively, MSG also induced brain damage. Histological examination of the hypothalamic sections from rat treated neonatally with MSG (4mg/gm body weight S.C. on alternating day for the first 10 days of life) revealed a lesion limited in the arcuate nucleus-median eminence region and a striking reduction in the number of arcuate neurons (Lamperti and Baldwin, 1979; Rodriquez-Sierra, et al., 1980; Terry, et al., 1981; Millard, et al., 1982; Antoni, et al., 1983; Katakami, et al., 1984). Furthermore, the optic nerve and chiasma were found smaller in MSG-treated rats than in control (Terry, et al., 1981: Antoni, et al., 1983).

It is well documented that the hypothalamus synthesizes and secretes various specific neurohormones, which are carried to the anterior pituitary gland via the hypophyseal portal vessels, where they exert stimulatory or inhibitory influence on the synthesis and release of the trophic hormones. Several important hormones are secreted by the anterior pituitary gland. The hormones of the pituitary play the major roles on the control of metabolic functions throughout the body such as GH, ACTH, TSH, Prolactin, FSH and LH (Guyton, 1991). GH promotes growth of the animal by affecting protein formation, cell multiplication and cell differentiation. FSH and LH control growth of the gonads as well as their reproductive activities.

Chemical or physical damage to the hypothalamus may thus result indirectly in changes in the contents and release of the anterior pituitary hormones and consequently, in changes in the weight of the respective target endocrine organ. Han, et al. (1965) demonstrated that hypothalamic lesion in weanling rats induced by bilateral electrolytic lesions technique caused obesity without overeating. The body fat content of the lesioned-rats was significantly higher than the control, whereas the nasoanal length and the femur length were significantly shorter than those of the control. The stomach weight was significantly less than those of the control and the pituitary of some lesioned-rats appeared to be smaller in size and atrophy.

Bernardis and Skelton (1966,1967) studied about growth and obesity in male and female rats after placement of ventromedial hypothalamic lesions at four different ages. They found that in terms

of Lee's index, all rats were equally obese when compared with their respective controls and the greater effect of ventromedial lesions in weanling rats was attributable to a greater vulnerability of the smaller brains in these animals.

Several lines of research suggested that adult rats and mice which received large doses of MSG as neonate showed a stunted linear growth, obesity and tail automultilation. The Lee's index, a measurement of body fat, was elevated in the MSG-treated group compared with the control. The femur and tibia lengths were shorter than the control group. Food intake was shown no significant difference or slightly hyperphagia in MSG treated rats compared with the control rats (Olney and Sharpe, 1969; Readding, et al., 1971; Araujo and Mayer, 1973; Nagasawa, et al., 1974; Tanaka, et al., 1978; Terry, et al., 1981). The other investigators showed that MSG injected neonatally significantly decreased pituitary, gonad, thyroid and adrenal weights in both sexes of rats (Redding, et al., 1971; Nemeroff, et al., 1978).

The cause of endocrine dysfunction may be disturbances in levels of anterior pituitary trophic hormones which are observed in adult rats treated with MSG as neonates and manifested arcuate destruction. Redding, et al. (1971) reported that daily injections of MSG beginning on the 2nd day of life resulted in a reduction of the pituitary contents of growth hormone (GH) and luteinizing hormone in rats at 40 day of age. Terry, et al. (1981) found that neonatally administered MSG caused a marked disturbance in episodic GH and prolactin (PRL) in adult rat. Both Bakke, et al. (1978) and Nemeroff, et al. (1977) also reported a decrease in serum GH. Moreover, studying in prepubertal

rats which had been given MSG as neonates by Dada, et al. (1984) found that GH cell size was reduced in both sexes although the individual GH cell contained normal amounts of GH.

Because GH secretion is believed to be regulated by two major hypothalamic factors ; one is inhibitory, somatostatin (SRIF) and the other, stimulatory, the GH releasing factor (GHRF), the alteration of both or one of these hormones is attributable to describe the abnormality of GH secretory pattern in MSG treated animals. Millard, et al. (1982) studied GH secretory mechanism in the rat using morphine sulfate (MS), a potent stimulant for GH. They concluded that GH deficit observed in MSG-treated rats was due to a relative loss of GHRF secondary to arcuate damage. Antoni, et al. (1983) studied the GH release induced by electrical stimulation and found that arcuate neurons were important in the maintenance of GH release. And then, by immunofluorescence technique, Bloch, et al. (1984) presented that GHRF-producing neurons were located mainly in the arcuate nucleus of rat. MSG treatment resulted in the complete loss of GHRF-immunoreactive cell bodies within this nucleus and provoked a selective disappearance of GHRF-immunoreactive fiber in the median eminence. On the other hand, SRIF is unlikely to be affected by MSG treatment because it had been reported that SRIF-containing cell bodies were located in the anterior hypothalamic periventricular area which was unaffected by MSG (Millard, et al., 1982).

As have been established, hypothalamus is the center for release of gonadotrophin-releasing hormone (GnRH) that controls the release of LH and FSH from anterior pituitary gland. GnRH presents

primarily in the mediobasal-hypothalamus, especially in the arcuate nucleus of this area. Therefore, it is believed that this nucleus controls most of female sexual activity (Guyton, 1991). So the selective effect of MSG that destroys the arcuate-nucleus therefore may be followed by the reproductive dysfuction.

The administration into adult rats of lower doses of MSG than those causing hypothalamic lesions, altered temporarily serum levels of anterior pituitary hormones (Nemeroff, et al., 1978; Olney, et al., 1976). Olney, et al. (1976) believed that subneurotoxic dose of MSG administered during growth and development may effect the endocrine system and have a cumulative effect on sexual development. However, the reproductive dysfuction resulting from neonatal treatment with MSG in dose that caused damage in arcuate nucleus has been reported to range from no effect to severe degree of reproductive disturbance.

There were many reports showing atrophy of ovary (Redding, et al., 1971; Holzwarth-Mcbride, et al., 1967; Bakke, et al., 1978; Rodriquez-Sierra, et al., 1980) and testis (Bakke, et al., 1978; Redding, et al., 1971) in animals which received MSG injection during neonatal period. While the reduction of pituitary and serum LH and normal level of FSH were found by other investigators (Lamperti and Baldwin, 1979), Bakke, et al. (1978) reported that normal serum FSH and slight increase of serum LH were found in both sexes of MSG-treated rats.

Pizzi and Barnhart (1977) reported that MSG administered during the neonatal period produced abnormal reproductive function in both male and female mice. The female animals treated with MSG

showed a delay in vaginal canalization, abnormal estrous cycle with prolonged estrous cycle and dominant in metestrus, fewer pregnancies and smaller litters, while male animals showed a reduced fertility. The MSG treated-mice also showed a decreased gonad weights.

In rats, Adamo and Ratner (1970) reported that adult female rats had normal vaginal cycles and the rats mated and produced normal litter after MSG neonatal injection while Trintini, et al. (1974) found that MSG caused earlier vaginal canalization and increased occurrence of estrus. Male and female treated-rats were fertilized and sexually active. Duration of pregnancy, delivery and number of litters were normal.

On the other hand, severe decline in fertility was observed by some investigators. Rodriquez-Sierra, et al. (1980) reported a delay in vaginal opening and decreasing percentage of rats ovulating in female rats. Moreover, they found that mean lordosis quality, an indication of the intensity of receptivity, was decreased in MSG-treated animals. Bakke, et al.(1978) observed that the percentage of pregnancy in MSG-treated rats was significantly reduced comparing with the control rats. Average birth weight of pups of these MSG-treated rats and number of pups per litter were also less than the control rats.