CHAPTER VII

GENERAL DISCUSSION AND CONCLUSION
It is well established that brain controls the release of hormones from the anterior pituitary by hypothalamic releasing and/or inhibitory factors. The hypothalamic releasing factors are mostly peptides having amino acids starting from 3-39. For eg., TRH (tripeptide), enkephalins (pentapeptide), cholecystokinin (octapeptide), LHRH (decapeptide), somatostatin (tetradecapeptide) and ACTH (39 amino acids). The extrapituitary localization of pituitary hormones is also known. Some of the hypothalamic peptide hormones such as somatostatin, TRH, CCK, LHRH have also been found in tissues other than the nervous system (Brazeau et al., 1973; Elde, 1979; Sharpe, 1980; Khodr and Siler-Khodr, 1980; Turkelson, 1981). The tripeptidized glutathione is ubiquitously localized in different tissues of the body and is present in brain (Meister and Anderson, 1983). Although metabolic functions of glutathione are known, its biological role as an antioxidant and as a substance in mopping the effects of free radicals is well established in many tissues (Flohe, 1979; Chance et al., 1979). Glutathione may particularly be helpful in preventing damage caused in the postanoxic period (Vali Pasha and Sadasivudu, 1984). However, not many studies are available regarding its biological role in central nervous system although it is the most simple tripeptide present in various tissues including the brain. The distribution of glutathione in different regions of the rat brain starting from 21 days to the adult period though found to be uniform, the glutathione content is significantly higher in hypothalamus reaching a peak at puberty. The striking increase in the glutathione levels at puberty suggest a possible involvement of glutathione in the events occurring during the onset of puberty. It is very interesting to note that intraventricular administration of glutathione stimulate the release of anterior pituitary hormones in appreciable
amounts. Glutathione at lower doses caused selective release of FSH when compared with the release of other pituitary hormones. The nearly four fold increase in FSH indicate that the tripeptide may have a role in FSH release. However, glutathione when injected in large doses cause release of other pituitary hormones as well. It seems to be highly potent in inducing GH release when given in higher doses. These results indicate that glutathione may be an important peptide, at least, in the release of FSH although both LH and FSH are controlled specifically by a single releasing hormone LHRH. The LH releasing potency of LHRH is more when compared to FSH (McCann, 1974; Ojeda, 1980). Although presence of a specific hypothalamic factor controlling FSH release has been suspected its isolation and chemical identity has not been successful (Lumpkin et al., 1980; McCann et al., 1983). LHRH and somatostatin given intraventricularly decrease glutathione levels in parallel with a rise in γ-glutamyl transpeptidase activity. The formation of γ-glutamyl dopamine by γ-glutamyl transpeptidase has already been reported (Tsuji et al., 1977; Ichinose et al., 1987). It is possible that the increased formation of γ-glutamyl dopamine in the hypothalamus under the influence of these hypothalamic releasing factors and may have a functional significance as dopamine has been shown to release anterior pituitary hormones (Vijayan and McCann, 1978c; Negro-Vilar et al., 1978b). Glutathione can also be utilized by other routes other than γ-glutamyl transpeptidase. The utilization of glutathione by transhydrogenase reaction in hypothalamus may have functional significance in that the disulfide peptide hormones such as vasopressin, oxytocin and somatostatin may be converted to compounds containing sulfhydryl groups thus altering their biological activity.
The role of FSH in gonadal function is well established. However, its extra pituitary localization particularly in brain is not known and much less about its role in behaviour. Intracerebral injection of FSH, curiously produced a decrease in hypothalamic glutathione content and changes in the content of glutamate and GABA the two potent neuroactive amino acids subserving a major proportion of synaptic function, during the onset of puberty without any significant change in post pubertal period. Such a role is suggestive of a functional and metabolic role for FSH in brain although the mechanism involved is not known. The decrease in the content of glutathione at puberty without any significant change in postpubertal period may be due to the involvement of glutathione in breaking down the disulfide bonds in the peptide hormones by transhydrogenase reaction. The increase in the total sulfhydryl groups content in hypothalamus under these experimental conditions lend support to such a contention.

Glutamate in brain has both a metabolic and functional role, about 60% of glucose carbon is known to be utilized for the formation of amino acids and in particular glutamate. Glutamate is one of the amino acids known to maintain functional integrity of the brain in the absence of glucose. Neuropharmacological studies indicate that glutamate is a neuroexcitatory substance. Furthermore, there is a close metabolic interrelationship between glutathione and glutamate in that the former may be a source for the latter and the latter may be involved in the synthesis of the former. Glutamate is also the precursor for GABA, a powerful neuroinhibitory substance which is also implicated in the activity of hypothalamic-hypophyseal axis (Vijayan and McCann, 1978a, 1978b; Negro-Vilar et al., 1980; Lamberts
et al., 1983; McCann et al., 1984). The significant increase in GABA levels in hypothalamus after the higher dose of glutathione administration would suggest that glutathione may be acting through GABA since earlier studies have clearly demonstrated that GABA in smaller doses is having a role in the release of LH and at higher doses released prolactin (Negro-Vilar et al., 1980). The significant increase in the levels of hypothalamic GABA observed after intraventricular injection of LHRH and after intraventricular glutathione administration suggest a functional interaction between LHRH, glutathione and GABA. One of the factors responsible for the significant increase in GH release following the administration of glutathione may be by the biological alteration of somatostatin through transhydrogenation by glutathione. The significant decrease in the content of glutathione following the administration of somatostatin provide proof to such a contention.

From the foregoing experimental observations and discussion it may be concluded:

1. that the pubertal spurt in the hypothalamic glutathione content and increased secretion of FSH following the intraventricular administration of glutathione together with the observation that the content of glutathione decreased following intraventricular LHRH and intracerebral FSH indicate a close interaction between glutathione, LHRH and the gonadotropic hormone FSH.

2. that GABA may be mediating the actions of glutathione and LHRH in hypothalamus since a significant increase in GABA was observed following intraventricular administration of glutathione and LHRH.
3. that glutathione may also be involved in the release of other anterior pituitary hormones such as prolactin and GH when administered in higher amounts.

4. that the release of Prl and GH by glutathione may be related to increased GABA in hypothalamus and probably by metabolic alteration of the disulfide peptide hormone somatostatin by trans-hydrogenation since under these conditions there is an increase in the total sulfhydryl groups.