Review of Literature
General Review

Ovarian hormones are among the many factors that influence appetite and body weight in female mammals (27,28). Appetite and energy intake in women fluctuate with phase of menstrual cycle, energy intake being consistently lower in the follicular relative to the luteal phase (29-35). However, the interpretation of these results is often difficult because there are variations in inter-subject cycle lengths (36) and the length of the luteal and follicular phase varies both between subjects and between cycles (36,37). Further, self-reporting (31,32), meticulous weighing of eaten food (29,33,34,35,38) may result in bias toward underestimation of habitual energy intake (39). Most of the studies have focused on normal weight women and the extent of change in cyclic hormone fluctuations in obese women may differ from this normal weight group (40). Though obese women usually exhibit normal concentrations of reproductive hormones, ovulatory dysfunction and amenorrhea are commonly reported especially, in women who have rapidly and dramatically increased body mass (40,41). Furthermore, cyclic changes in ovarian hormones across the menstrual cycles are associated with several hormonal fluctuations and their concomitant physiological affects. Hormonal changes include fluctuations in catecholamines (noradrenaline, adrenaline and dopamine) (42) adrenocorticotropic hormone (ACTH), cortisol, growth hormone, thyroid hormones (43,44) and endogenous opioids (45) and there is increase in food intake when concentrations of these hormones elevated but there was no direct measurement of hormone concentrations in previous studies and data might not represent the menstrual phase to which it has been attributed to (3).
Most of the research pertaining to gonadectomy and hormone replacement has been performed with albino rats and this may be because of the above mentioned methodological variations and other confounding factors in women. Female rats also show phase related changes in food intake and body weight (9-12) and decreased plasma estrogen to a negligible level in ovariectomized female rats (14), which results in increase in FI, WI and BW, while estrogen substitution reverses either centrally (15) or peripherally (16), suggesting that lack of estrogen causes abnormal increase in ingestive behaviors and body weight in female rats similar to postmenopausal women. Moreover, it has been reported that administration of estradiol to gonadally intact female rats can result in pseudopregnancy and weight gain (46,47). Therefore, in the present study, we have used ovariectomized animals as ovariectomy in female rats provides a useful model (17) to understand the role of gonadal hormones and their role in the pathophysiology of overeating and body weight gain in postmenopausal women.

In female rats, FI, BW, body temperature and physical activity fluctuates with the estrous cycle i.e., they are low during estrus than diestrus (9). The principal ovarian hormonal modulation of energy balance in female rat appears to be accomplished by secretion of estrogens (48). However, only in the presence of estrogens (gonadally intact females or in ovariectomized rats given estradiol), progesterone treatment with high doses (5mg/day) unequivocally raises the food intake and body weight (49,50).

Following ovariectomy, female rats overeat and gain weight rapidly for approximately one to two months. Then hyperphagia subsides, and body weight is maintained at 20-25% above that of intact control animals (16,51).
The converse happens when these rats are treated with estradiol i.e., a transient hypophagia and permanent (as long as estradiol treatment continues) body weight loss (52). On the other hand, progesterone had no effect on FI, voluntary exercise, BW, or carcass composition in ovariectomized rats (49,53,54,55). It has been suggested that the effects of ovariectomy and progesterone treatment appear to be similar and non-additive, which may suggest that ovariectomy and progesterone treatment cause essentially the same physiological response, which can occur only once (49,53).

It has been reported that estrogen is more effective in preventing rather than reversing weight gain associated with OVX-induced obesity (56). Since both ovariectomy and estrogen induced changes are transient on FI and sustained effect on BW, the hormone-induced alterations in FI have been viewed as regulatory behaviors, which serve to align body weight or fat content weight with a hormonally dictated set point (46). Consistent with this proposed regulatory role of estradiol are the numerous reports that the effects of estrogens on feeding and BW depend on the animal's degree of obesity at the time of treatment. The heaviest rats show the greatest anorexia (hypophagia) and weight loss (51,57) and very lean animals may show no decrease in FI and BW when given estradiol (58,59). Interestingly, it has been demonstrated that taste aversion is not a mediator for the suppressive effects of estrogen on FI and BW in female rats (60) as previously reported (61,62).

Similar to FI and BW, spontaneous WI as well as angiotensin-induced thirst also fluctuates during the estrous cycle, with intake being lowest on the day of estrus when estrogen exerts its behavioral and physiological actions.
and ovariectomy abolishes this fluctuation (11,12). The acute administration of estrogen decreases spontaneous (11) as well as polyethylene glycol-induced (63) water intake in ovariectomized female rats. However, the mechanisms governing WI are not known. Estrogen decreases WI induced by water deprivation and this is in contrast to results of previous studies (64,65). Estrogen also reduces WI, stimulated by isoproterenol (ISOP) administration but not hypernatremia (66) and the effect of estrogen on stimulated WI is specific to that in response to activation of peripheral renin-angiotensin system (RAS) (66). Estrogen but not progesterone in physiological doses has been shown to attenuate WI induced by intraventricular injection of angiotensin II in a dose dependent and reversible manner demonstrating the central interaction between angiotensin II and estrogen (21). Early works have suggested that estrogens may influence body fluid regulation by interacting with several neurotransmitters, including serotonin, dopamine and noradrenaline (67).

On the other hand, dopamine (DA) plays an important role in the regulation of feeding behavior (68) and factors such as brain area, dose used etc influence this behavior. It inhibits feeding in the perifornical hypothalamus and stimulates in the lateral hypothalamus (69) and DA in low levels enhances and whereas in high doses cause inhibition of feeding (70,71). Yet, DA is usually accepted as an inhibitory neurotransmitter in the control of feeding behavior (72,73). DA exerts its inhibitory effect via DA receptors (74). There are several subtypes of DA receptors (D1, D2, D3, D4 and D5) (75) and broadly classified as D1-like (D1 and D5) and D2-like (D2, D3 and D4) subtypes on the basis of physiological, pharmacological and biochemical
studies (76). Earlier studies have reported that both general and specific D1 and D2 agonists could decrease FI (77,78) and co-administration of these agonists also additively decrease the daily FI, BW, and hypothalamic NPY levels in rats (69). Further, positron emission tomography (PET) studies have revealed that pathological overeating and obesity are associated with significant reduction in DA D2 receptors in the striatum of obese individuals than normal individuals (79).

The possible mechanisms and related neurotransmitters that mediate these estrogen actions on ingestive behaviors and body weight regulation are still unclear. It has been suggested that neurons located in the hypothalamus or other brain regions modulate estrogen receptor mRNA expression through the synthesis and release of many regulatory neurotransmitters (80). Previous studies have shown that estrogen exerts its anorectic and weight reducing actions via many peptides. In the female rat, ovariectomy decreased and 17β-estradiol substitution restored neuropeptide- Y (NPY) levels selectively in the arcuate nucleus (ARC) and ventromedial nucleus of hypothalamus (81). Further, it has been reported that inhibition of FI and BW gain induced by estradiol treatment in ovariectomized rats is due to decrease in NPY levels in paraventricular nucleus (PVN) but not in VMH (17,82). Others have reported that estradiol treatment increases satiating potency of cholecystokinin (19) and of glucagon (20). Contradictory findings have been reported on serum leptin levels, as increased (18,83), decreased (84) or not altered (85) following ovariectomy. Earlier, it has been demonstrated that elevation of BW and serum leptin levels in ovariectomized rats were blocked by physiological
Review of Literature
doses of estradiol (86). Moreover, estrogen also modulates WI in ovariectomized rats via the peptide hormone, angiotensin-II, (21).

Previous studies have suggested that the direct actions of estradiol on central dopaminergic system may be critical to control the FI and BW (3). It has been demonstrated that secretion of dopamine into hypophysial portal blood varies throughout the estrus cycle and is lowest during proestrus (87). There are conflicting reports in which fluctuations in the dopamine content was detected after long term ovariectomy and estrogen replacement but not during the estrus cycle (88). Estrogens have also been found to inhibit FI presumably by inhibiting the activity of dopamine beta-hydroxylase thereby causing a decrease in norepinephrine levels (89) suggesting the possible interaction between estrogen and dopamine in regulating feeding behavior and body weight.

The present study investigates the possible role for dopamine in mediating estrogen effects on ingestive behaviors and body weight because both estrogen and dopamine participate in the regulation of these behaviors as reported in the literature. Further evidence for our present hypothesis comes from the earlier findings that suggested, the down regulation of D2 receptors may represent a common pathogenic mechanism contributing to obesity (90) and addiction to various types of drugs including cocaine (91) alcohol (92) and opiates (93). Further, it has been reported that pathological overeating and obesity are associated with significant reduction in D2 receptors in the striatum of obese humans (79) as well as rats (94) compared to controls. On the other hand, sulpiride (D2 receptor antagonist) induced body weight gain and obesity in females rats totally prevented by D2 agonist
bromocriptine (26,95) or estradiol (25) or tamoxifen (95) administration. Tamoxifen acts as estradiol with respect to FI and BW (96). Interestingly, it has also been demonstrated that bromocriptine treatment significantly reduces body fat stores in postmenopausal women (97).

Earlier studies have revealed the presence of estrogen and dopamine receptors in VMH, NSL and BLA (98-103). Estrogen in VMH and NSL is reported to be involved in regulation of ingestive behaviors and body weight (104,105). Corticomedial nucleus of the amygdala has been involved in the estrogenic modulation of ingestive behaviors (106), but the role of BLA is not yet to be established. Therefore, we have tested the hypothesis whether estrogen interacts with dopamine in regulating FI, WI and BW in VMH, NSL and BLA in ovariectomized rats.

Ventromedial hypothalamus

General role of VMH on FI, WI & BW

Previously, it has been reported that stimulation of the ventromedial nucleus of hypothalamus (VMH) causes inhibition of feeding and reduced weight gain (107-109), whereas, unilateral (110-112) or bilateral electrolytic lesions in this region produce hyperphagia and obesity (113-116). However, the neurotransmitters or neuromodulators responsible for the mediation of these ingestive behaviors and body weight still remains obscure. Extensive studies on this problem have highlighted the importance of the increased circulating concentration of insulin and disturbances in the function of the autonomic nervous system for the development of this syndrome (114,116-119). There is an increased firing rate of the vagus nerve (120) and a reduced firing rate of the sympathetic nerves (120,121) with reported reductions in activity of the
Review of Literature

thermogenic properties of brown adipose tissue (122,123). In VMH lesioned rats, the hypothalamic contents of norepinephrine (NE) and dopamine (DA) were selectively decreased, but acetylcholine (ACh) and serotonin (5-HT) levels were not changed from those in controls (124). However, some authors have attributed the electrolytic VMH lesion-obesity, in part to tissue ablation and in part to metallic ion deposits stimulating (rather than disinhibiting) vagally mediated insulin responses (125). Further, it has been reported that hypothalamic lesions that do produce obesity, damage the nearby ventral noradrenergic bundle or its terminals (126). In contrast, later studies have demonstrated that hypothalamic hyperphagia and ventral bundle hyperphagia are two different syndromes (127). Leptin receptors expressed in the VMH have also been implicated in the regulation of feeding behavior and energy balance (128) and leptin inhibits neuropeptide Y (NPY), a potent orexigen, which appears to be a key component by which leptin regulates body weight (129).

Effect of estrogen in VMH on FI, WI and BW

The highest numbers of estrogen concentrating cells were found throughout the extent of the VMH (98,130), which supports the notion that this region is an important target site for the actions of estrogen in behavior and neuroendocrine functions in female rats. While, a phase dependant change in estrogen mRNA expression in the brain was observed during the estrous cycle, the magnitude and direction of change were regionally specific. The level of expression in VMH was low during estrus and gradually increased throughout the cycle until it peaked at proestrus, a period during which circulating estrogen levels are known to increase (131,132). The number of estrogen receptor-beta (ER-β) immunoreactivity cells in the VMH increased
caudally with only a few scattered labeled cells present in the rostral portion of the ventral subdivision of the VMH and many labeled cells present in the caudal portion of this region. Additional immunoreactive cell nuclei were also detected in the caudal and basolateral portion of the VMH (133). Expression of ER-\( \beta \) mRNA and protein is less in VMH when compared to ER-\( \alpha \), indicating that ER-\( \beta \) plays a limited role in the central regulation of procreation and reproduction compared with that of ER-\( \alpha \) (134). However, studies have shown that ER-\( \beta \) in the central nervous system is involved in the anorectic action of estrogen (135).

Many researchers have reported a sex difference in the weight gain induced by VMH lesions; i.e., females gain more weight than males (136-141). It has been demonstrated that VMH has a high density of estrogen binding neurons (98,142), and pure crystalline (undiluted) implants of estrogen acts on the ventromedial hypothalamic nuclei to reduce FI and BW (104,15). In contrast, later studies have reported that crystalline implants of estrogen in VMH did not have any inhibitory effect on FI and BW (143,144). Moreover, pure crystalline estrogen injected in the area of the brain spreads to systemic circulation leading to peripheral effects such as increased estrus vaginal smears or uterine weights (143,144). Therefore, the later studies have adapted dilute estrogenic stimulation to study the actions of the estradiol that restricts steroid diffusion within the brain (143,145,146). On the other hand, it has been reported that presence of cornified vaginal smears was not associated with significant impact on FI and BW or lordosis and peripheral changes produced by leakage from the central implant sites were neither necessary nor sufficient to account for the observed behavioral changes (143).
Previous studies have demonstrated that peripheral estrogen is sufficient to prevent the increase in FI and BW in ovariectomized rats (147-149). However, there is some inconsistency in the literature as to whether rats with VMH lesions capable of gaining extra weight and also whether the peripheral EB could still be able to inhibit FI both in VMH lesioned and non-lesioned rats (150,151). Others have found that the attenuation of estradiol effects at normal weight levels involves CNS sites other than VMH, or possibly metabolic effects that could influence FI and BW (152). For instance, it has been reported that insulin was metabolized rapidly, during high plasma estradiol concentrations (153). Others have reported that estrogen may account for the reduced gluconeogenesis, enhanced glycogen storage, increased extrahepatic peripheral metabolism, and hyperinsulinemia (154,155). Estrogen also influences hepatic estrogen receptors (156) and adipose tissue (7). In contrast, the effects of ovariectomy and estradiol replacement on FI and BW are not attenuated in streptozotocin-diabetic rats maintained with constant daily insulin therapy (157), indicating that ovarian hormones affect eating and body weight in the absence of changes in pancreatic insulin output (158). Estradiol treatment does not alter FI and BW responses to either acute or chronic insulin treatment in ovariectomized rats (157), suggesting that altered tissue responsiveness to insulin or even other peripheral effects may not be the basis for the body weight and appetite suppressing actions of estradiol. From these conflicting reports, it is difficult to infer that estrogen in the VMH does not have any role in FI, WI and BW. Therefore, the present study tested the effect of direct microinjections of
diluted estradiol benzoate (EB) into VMH and also the subcutaneous injections of EB with and without lesion of the VMH on these behaviors.

Effect of dopamine in VMH on Fl, BW and WI

In normal rats, the highest expression of dopamine D2 receptors was found in VMH and lateral hypothalamic area (LHA) whereas dopamine D1 receptors expression was low in both the nuclei (99,100). The normal function of dopaminergic transmission in VMH is indispensable for feeding and survival (159). One study has shown that iontophoretic application of dopamine decreases the electrical activity of the majority of the VMH neurons (160). On the other hand, dopamine acting locally within the hypothalamus, acts as a potent inhibitor of feeding in perifornical area, ventromedial hypothalamus and arcuate nucleus (161,162). Previous workers have reported that dopamine D1 (SKF-38393) and D2 (bromocriptine) receptor agonists decrease Fl and BW (69,163,164). Bromocriptine (BC) ameliorates BW, hyperinsulinemia, insulin resistance, or glucose intolerance (165-167) and these actions of BC on metabolism are mediated either by central via VMH (164) or peripheral (165) mechanisms. However, later it has been shown that peripheral responses are not necessary for bromocriptine to affect on body weight gain, hyperinsulinemia, insulin resistance, or glucose intolerance (163). Moreover, bromocriptine significantly reduces weight gain without affecting food consumption (163). In vivo microdialysis study has shown that in the normal rat, the release of dopamine in the LHA and VMH correlates with meal size (MZ) and postmeal intervals, reflecting the meal number (MN) (168,169).

It has been reported that dopamine inhibits significantly more VMH neurons in obese than normal rats and D2 receptors in the VMH are reported
Review of Literature

to mediate inhibition of FI (170). Further, it has been demonstrated that in obese Zucker rats, there is an up-regulation of D1 receptor mRNA in VMH and adenohypophysis (AH), however, down-regulation in LHA. D2 receptor mRNA was down regulated in both VMH and LHA but no change in AH, compared to lean rats. Low D2 receptor expression in VMH induces hyperphagia, and FI after sulpiride (selective D2 receptor antagonist) injection was greater in obese rats but had no effect on lean rats (90) indicating the strong D2 receptor involvement in the regulation of ingestive behaviors and body weight regulation in VMH.

Previous studies have demonstrated that dopaminergic D1 and D2 receptor mRNA in the hypothalamus were highly expressed in anorectic tumor bearing (TB) rats compared with non-tumor bearing (NTB) free feeding normal rats suggesting that up regulation of these receptors may be associated with decrease in food intake (171). Furthermore, the intra-VMH injection of the D1 receptor antagonist in tumor bearing rats (TB-SCH-23390) led to significant and persistent decrease in FI whereas it had no effect on in the non-tumor bearing free feeding rats (NTB-SCH). The injection of intra-VMH D2 receptor antagonist sulpiride significantly stimulated FI in the tumor bearing rats relative to their control i.e., tumor bearing sulpiride control (TB-SC). In non-tumor bearing free-feeding rats (NTB-Sul), intra-VMH sulpiride also increased FI significantly compared to baseline intakes (172). Obese and diabetic animal models have increased VMH noradrenergic and serotonergic activities (164,173-176) and decreased brain dopamine synthesis (173) relative to normal animals, suggesting central mechanisms. Further, spontaneous feeding is in obese Zucker rats accompanied feeding related differences in
Review of Literature

monoamine profile (5-HT and DA) compared to the normal Wistar rats (177).

In VMH lesioned rats also, the hypothalamic contents of norepinephrine (NE) and DA were selectively decreased suggesting that a disturbance of NE and DA neurons in the hypothalamus is involved in the development of VMH lesion-induced obesity (124).

Based on the evidences reported above, dopamine and its receptors (D1 and D2) in VMH appear to be involved in the regulation of feeding related behaviors and body weight, in normal and pathological conditions. However, it is not known whether similar neurochemical alterations in VMH would account for the ovariectomy induced effects on ingestive behaviors and body weight in female rats. Therefore, in the present study we have examined the role of dopamine D1 and D2 agonists and antagonists on these effects, in ovariectomized female rats.

**Estrogen-dopamine interaction in VMH**

Neurons, located in the hypothalamus or other brain regions, modulate estrogen receptor mRNA expression through the synthesis and release of regulatory neurotransmitters and these neurotransmitters could interact with estrogen receptor neurons and initiate a cascade of events that result in estrogen receptor gene regulation (80). For instance, the afferent inputs that release norepinephrine, may modulate estrogen receptor synthesis in the hypothalamus (178) and it is also possible that other neurotransmitters i.e. dopamine, neuropeptide-Y, serotonin, etc. might play a role in transsynaptic regulation of the estrogen receptor gene (80). Previous studies have shown that estrogen (15,104) and bromocriptine (69,163,164) suppress FI and BW in VMH. Since, both dopamine and estrogen have inhibitory effects on ingestive
behaviors and body weight, we speculate that dopamine in VMH would play a crucial role in estrogen mediated effects on FI, WI and BW in ovariectomized rats.

**Nucleus septal lateralis**

**Effect of estrogen in NSL on FI, WI and BW**

Although, the nucleus septal lateralis (NSL) does not reach the overall density of VMH, autoradiographic and biochemical studies have demonstrated estradiol concentrating cells more reliably and heavily in the lateral septum (98,130). Spontaneous activity of neurons in the lateral septum is increased at proestrus and estrus after estrogen treatment in ovariectomized animals (179). Further, estrogen receptor-beta (ER-β) immunoreactivity was also detected in the lateral septum but a few cells present compared to medial septum (133).

NSL appears to be an important extra-hypothalamic region involved in the regulation of energy balance in the female rat (180). It has been reported that kainic acid and domoic acid lesions of the NSL produce a significant increase in body weight in female rats but not in male rats (141,180-182). NSL is sexually dimorphic with respect to its role in neural control of body weight regulation (181). Further, kainic acid lesions of the septum also resulted in increase in FI along with BW, and attenuation of anorexic effects of estrogen on FI and BW (180). Septal lesions with kainic acid produce hyperdipsia, (183) and the magnitude of the kainic acid induced increase in WI were comparable to that seen after large electrolytic lesions of the septum (184-187). However, the mechanisms by which exogenously administered estrogen reduces FI and BW with electrolytic lesions in lateral septum are not
known. Moreover, there was no literature to demonstrate the direct central injection of estradiol benzoate (EB) into the NSL on FI, WI and BW in ovariectomized rats. Therefore, we have investigated the role of NSL in mediating EB induced effects on FI, WI and BW in ovariectomized rats.

**Effect of dopamine in NSL on FI, BW and WI**

There is a discrepancy in the presence of dopamine receptors in the lateral septum. One study has shown low but consistent levels of binding (101), high density of labeling for dopamine D2 receptors (188) while others have reported lower levels of both D1 and D2 in the lateral septum (189).

It has been demonstrated that electrolytic lesions in the lateral septum increased, and kainic acid septal lesions decreased female sexual behavior. Dopamine levels in the striatum showed highly significant inverse correlation with the lordotic behavior of estrogen primed rats; i.e., the higher animal's lordotic quotient, the lower was its brain levels of DA levels (105). However, there are no studies as to what role does dopamine and its receptors play in NSL with respect to FI, WI and BW in ovariectomized female rats. Earlier, from our laboratory, it has been reported that NSL lesion increased WI, where DA had no role on WI (190). As NSL contains a variety of neurotransmitters, (191-194) their functional significance of these neurotransmitters, especially the role of estrogen and dopamine on ingestive behaviors and body weight was tested in the present study.

**Estrogen-dopamine interaction in NSL**

To our knowledge, there are no reports regarding the interaction between estrogen and dopamine in NSL on ingestive behaviors and in the regulation of body weight. Therefore, we have investigated the role of
dopamine in estrogen mediated effects on FI, WI and BW in ovariectomized rats.

**Baso lateral amygdala**

**General role of BLA on FI, WI and BW**

Numerous studies have shown that amygdala plays a crucial role in feeding and drinking behaviors (195-201). Bilateral temporal damage or temporal lobectomies resulted in hyperphagia and obesity both in monkeys and human beings (202-205). However, dorsomedial lesions in dogs and cats (medial and central) have resulted in both aphagia and weight loss (195,206) and hyperphagia and obesity (207). While, lesions of the lateral or basolateral group of nuclei have resulted in no change (195) or hyperphagia and obesity (208-210). Similarly, the studies on rats have produced inconsistent and conflicting reports with amygdaloid lesions in which, large lesions that destroy most of the amygdala resulted in hypophagia and weight loss (195,211,212). On other hand, the rats with smaller lesions aimed at basolateral and or lateral nuclei resulted in weight gain (196,213,214), no change in body weight (215-219) or even weight loss (195); similarly, contradictory results have been reported with respect to corticomedial and central nuclei (199,218). However, there was profound decrease in FI and BW with lesions in the central amygdaloid nucleus in rats along with sensory-motor deficits, including excessive gnawing and spillage of their food pellets (213). Aphagia following lesions of the medial and central nuclei has been attributed to additional damage to adjacent nonamygdaloid structures involved in sensory-motor functions. Lesions which spare caudal globus pallidus (219-222) did not result in decreased feeding behavior, weight loss or sensory-motor deficits,
demonstrating that aphagia is a consequence of damage to the globus pallidus (219, 223-226).

Hyperphagia and obesity of amygdala lesions indicate that normally amygdala is inhibitory for feeding and body weight, but it can be ruled out as medial, central nuclei compared to the basolateral complex of nuclei have entirely different embryonic origins (227) or diverse lesions might have been damaged a critical area and this critical area could be posterodorsal amygdala [(posterodorsal medial nucleus, bed nucleus and striaterrinis) (228)]. Many studies have reported that posterodorsal amygdala (PDA) lesions resulted in hyperphagia and obesity (110,229-232). Few studies in rats demonstrated hyperphagia and weight gain with BLA or lateral lesions that were either very dorsal or posterior (196,213,214,228,233). In one study, it has been reported that basolateral lesions resulted in small weight gain in young male rats without typical weight gain with sham lesions (213) unlike in other studies in which it was found that sex-specific weight gain occurred with sham lesions (232). However, most studies that have examined bilateral electric lesions of the basolateral nuclei in male rats did not find excessive weight gain (215,217-219) although, other studies did (196,199,214,) and female rats with BLA lesions evidenced some weight gain, as they weighed more than sham operated controls. However, histological analysis of brain sections has indicated that the weight increase resulted from slight invasion into the PDA (234). The functional disruption of BLA (235,236) resulted in conditioned taste aversion (CTA) but not the other nuclei of amygdala (235,237,238) and also neophobia (234). Rats that received lesions to the PDA gained significantly more weight than the rats with BLA lesions and behavioral deficits such as
CTA and neophobia were more pronounced with BLA lesions and they were not produced by PDA lesions, whereas, weight gain that resulted with PDA lesions were not found with BLA lesions (234).

An inhibitory mechanism may be located in the posterior amygdala, and lesions of this area increases WI, whereas, electrical stimulation produces hypodipsia (199). However, there are inconsistencies with regard to the effect of BLA lesions on drinking behavior. For instance, after electrolytic lesions of the BLA, WI was found to be unchanged (239,240), increased (241,242) or decreased (243,244). Further, lesions in the BLA also resulted in increased WI (213,245), suggesting that normally BLA exerts inhibitory effect on drinking behavior.

**Effect of estrogen in BLA on FI, WI and BW**

The medial and cortical amygdaloidal nuclei are the most densely labeled, and BLA cells have few labeled estrogen neurons (98,130). In the amygdala, estrogen receptor- beta (ER-β) immunoreactivity cell nuclei were abundant in the medial, cortical, central and amygdalohippocampal subdivisions, whereas, fewer cells were present in the lateral nuclei (133). However, subsequent comparative studies revealed that ER-β immunoreactivity is high in females than in males, ER-β protein and mRNA expression was higher in the lateral amygdaloid nucleus compared to medial amygdaloid complex (134). Wide distribution of ER-β mRNA has been reported in BLA (246).

Amygdala also takes up estradiol and affects feeding. It has been reported that hyperphagic rats with amygdaloid lesions are similar in some respects (e.g., lack of finickiness) to ovariectomized rats (247). Moreover,
previous pharmacological studies have shown that the medial amygdala is sexually dimorphic (248). It has been reported that there is a sex difference in weight gain after PDA lesions independent of estrogen levels. However, the weight gain produced by amygdaloid lesions and ovariectomy were additive (232). Few studies have reported that in female rats, estradiol benzoate (EB) implanted into the cortical amygdala can reduce FI (106) and others have reported that medial amygdala may monitor estradiol levels in the blood and cerebrospinal fluid and may send information about the stage of the estrous cycle to modulate gonadotropin release and feeding in female rats (250) but not in the BLA. Therefore, we have investigated the role of EB (both peripheral and central injections) in BLA on FI, WI and BW in ovariectomized rats.

**Effect of dopamine in BLA on FI, BW and WI**

An autoradiographic study, using specific D1 receptor antagonist SCH-23390 has revealed intermediate labeling of D1 receptor in BLA (102) whereas, D2 and D3 receptors and their mRNAs are co-localized in basolateral and basomedial amygdala (103). DA terminals in both the medial prefrontal cortex (mPFC) and nucleus accumbens (NAC) of the rat play an important role in the attribution of incentive value to sensory properties of biologically relevant stimuli and facilitate appropriate behavioral responses (251). It has been reported that administration of lidocaine into the central amygdaloid nucleus significantly attenuated feeding-evoked increases in dopamine efflux in both terminal regions of mPFC and NAC. These neurochemical effects were accompanied by feeding-related behaviors akin to the Kluver-Bucy syndrome. In contrast, inactivation of the basolateral part
affected neither FI nor dopamine efflux in the NAC, but triggered dramatic long-lasting oscillations in dopamine efflux in the mPFC, irrespective of whether food was presented or not (252). Therefore, the present study tested the role for dopamine in BLA on FI, WI and BW in ovariectomized rats.

**Estrogen-dopamine interaction in BLA**

Previous studies have shown that bilateral injection of 6-hydroxydopamine (6-OHDA) into BLA in cycling rats resulted in significant decrease of NE and DA in right and left amygdaloid lesioned animals compared to sham lesioned animals, but hypothalamic levels of NE and DA were not different between the groups. Serum estradiol concentrations were significantly lower in lesioned animals than in controls. The data suggest that the amygdaloid catecholaminergic systems exert an inhibitory effect on catecholamine content of the adrenals and the ovary, and influence the ovarian estradiol secretion mechanism (253).

However, there are no reports regarding the possibility of interaction between estrogen and dopamine in BLA which might influence ingestive behaviors and weight regulation in ovariectomized rats. Therefore, we have tested the role for dopamine in estrogen mediated ingestive behavior and body weight regulation in BLA.