CHAPTER I

INTRODUCTION

Anxiety disorders, the most common psychiatric illness, affect an estimated 3 to 8 of every 100 of the population (Kessler *et al.*, 1994). They may develop from a complex set of risk factors, including genetics, brain chemistry, personality, life events, and sex. However, the basic knowledge of these disorders, the mechanisms of etiology, and the treatment regimen are still unclear.

Gender discrepancy has been recognized in anxiety disorders, and most studies indicate that more women than men suffer from these disorders (reviewed by Palanza, 2001). The ovarian hormones fluctuations may lead to behavioral changes that may be related to anxiety in women. Recently, several groups reported the differential anxiety-like behavior of the female rats in different phases of estrous cycle (Diaz-Veliz *et al.*, 1997; Marcondes *et al.*, 2001). They demonstrated that the proestrous phase, which has the highest plasma estrogen levels, had lower levels of anxiety than other phases. Moreover, treating diestrous female rats with estrogen can abolish the difference in the levels of anxiety in proestrus and diestrus (Marcondes *et al.*, 2001). It thus seemed likely that estrogen might produce the anxiolytic response during the estrous cycle of the rats. In addition, the menopausal women showed symptoms of impaired cognitive function, depression, and anxiety (Arpels, 1996; Campbell and Whitehead, 1977; Sherwin, 1998) which were improved with estrogen replacement therapy. The consistent data of chronic estrogen treatment in the ovariectomized (Ovx) rats using the elevated plus-maze (EPM), also manifested an anxiolytic property (Frye and Walf, 2004; Koss *et al.*, 2004; Pandaranandaka *et al.*, 2006). All of these demonstrated an important role of estrogen on the regulation of anxiety levels.

The etiology of anxiety disorders have been related to the abnormalities of the serotonergic system (Lopez-Ibor, 1988). Drugs which are effective in the treatment of anxiety mostly act on this system, such as selective serotonin reuptake inhibitors (SSRIs), 5-HT$_{1A}$ receptor agonists, 5-HT$_2$ receptor antagonists, monoamine oxidase inhibitors (MAOIs) and 5-HT-precursor, 5-hydroxy-L-tryptophan (reviewed by Hashimoto *et al.*, 1999). Interestingly, the numbers of studies have addressed the relationship between estrogen and serotonergic system.

Estrogen receptor-β (ER$_β$) mRNA has been reported the localization in the dorsal raphe of the rat (Shughrue *et al.*, 1997). In addition, ER$_β$ protein was also found in the raphe nuclei (Gundlah *et al.*, 2001) and various brain areas, including amygdala, hippocampus, and frontal cortex (Shughrue and Merchenthaler, 2001). Estrogens have also been shown to regulate some components of the serotonergic system such as the 5-HT$_{1A}$ receptor (Osterlund *et al.*, 1999), 5-HT$_{2A}$ receptor (Cyr *et al.*, 1998) and serotonin reuptake transporters (SERT) (McQueen *et al.*, 1997) in brain regions involved in control of mood, mental state, cognition, emotion, and behavior.

The evidences indicated that anxiety, as defined in a given animal model, may differ from that generated in other models depending on its nature (innate or learned), its response to the effects of drugs and environmental manipulations, and its underlying neural substrate (Handley and McBlane, 1993; Zangrossi and Graeff, 1997). The elevated T-maze (ETM) (Graeff *et al.*, 1993; Viana *et al.*, 1994; Zangrossi and Graeff, 1997) can generate two types of fear (i.e. innate and learned) in the same rat with one experimental session. It was developed based on Deakin and Graeff (1991) hypothesis of the opposed role of serotonin in generalized anxiety disorder (GAD) and panic disorder (PD). Briefly stated, they proposed that serotonin, whereas inhibiting the expression of panic-like responses (e.g. escape) by acting in the dorsal periaqueductal gray (PAG), facilitates more flexible and coordinated defensive reactions (e.g. inhibitory avoidance) by acting in structures such as the amygdala and frontal cortex. Since the latter behavior strategies usually involve learning and memory, they represent conditioned anxiety and may be related, in clinical terms, to GAD. As a consequence, the ETM was intended to generate, in the same rat, inhibitory avoidance and one-way escape behaviors. So far, reported drug effects on these tasks have largely supported the proposed relationship of these responses to GAD and PD, respectively (Graeff *et al.*, 1993, 1998; Teixeira *et al.*, 2000; Viana *et al.*, 1994).

Therefore, the objectives of present study were, as follows:

1)   To determine the effects of estrogen on the anxiety-like behaviors of the female rats placed on the ETM.

2)   To examine the modulatory effects of estrogen on the serotonergic neurotransmission (i.e. serotonin and its metabolite levels; tryptophan hydroxylase enzyme and SERT protein levels).

3)   To examine the effects of estrogen on the postsynaptic serotonin receptor function on the anxiety-like behaviors tested with the ETM.

This study would provide more information concerning the role of estrogen in regulating anxiety levels. Moreover, the information could also be used as supportive information for the treatment of anxiety disorders in women.