INTRODUCTION
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Steroids were reported to influence brain excitability as long ago as 1942 (Selye, 1942). However, it was not until 1984 that the synthetic steroid alphaxolone was electrophysiologically demonstrated to potentiate γ-aminobutyric acid (GABA)-gated Cl⁻ conductance (Harrison and Simmonds, 1984). Subsequent studies determined that the progesterone metabolite allopregnanolone (AP) (3α-hydroxy-5α-pregnane-20-one) and the deoxycorticosterone metabolite allotetrahydrodeoxycorticosterone (THDOC) (3α,21-dihydroxy-5α-pregnane-20-one) were potent GABA-agonist modulators of the GABA-A receptor complex via a stereospecific interaction at a unique steroid recognition site associated with the GABA-A receptor complex (Belelli et al., 1990; Paul and Purdy 1992; Lambert et al., 1995). Radioligand binding and electrophysiological studies indicated that these steroids enhance binding of [³H]flunitrazepam, a benzodiazepine (BZD) and [³⁵S]f-butylbicyclophosphorothionate (TBPS), a convulsant, to the GABA-A receptor, and also enhance GABA agonist-induced increases in ³⁶Cl⁻ flux from synaptoneurosomes (Majewska et al., 1986; Marrow et al., 1987; Harrison et al., 1987; Majewska, 1992; Hawkinson et al., 1994a,b). These in vitro demonstrations provide evidence that some steroid metabolites have rapid membrane actions that are distinct from the genomic action of classical steroid hormones.

Subsequently, the term "neurosteroid" was coined in 1981 by Etienne-Emile Baulieu to refer to those steroids that are both synthesized in the central nervous system (CNS), either de novo from cholesterol or from steroid hormone precursors, and that accumulate in the nervous system to levels that are at least in part independent of steroidogenic gland secretion rates (Baulieu, 1981, Hu et al., 1987b; Jung-Testas et al., 1989b; Baulieu and Robel, 1990). The term "neuroactive steroid" refers to both endogenous and synthetic steroids that rapidly alter CNS excitability. During the last decade, several neuroactive steroids has been identified and characterized with in the brain (Robel and Baulieu, 1994;
Mellon, 1994). Robel and Baulieu (1994; 1995a,b) characterized several neurosteroids in animal as well as human brain at concentrations independent of their plasma levels. These steroids appeared independent of gonadal and adrenal synthesis, since they persist after adrenalectomy and gonadectomy or after pharmacological suppression of adrenal and gonadal secretions. The reduced metabolite of progesterone, AP is the first neurosteroid that has been extensively characterized in the CNS. Subsequently, several neuroactive steroids such as pregnenolone, pregnenolone sulfate (PS) (5-pregnen-3β-ol-20-one sulfate), progesterone, dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate (DHEAS) (Δ5-androsten-3β-ol-17-one sulfate) have been characterized in the central and peripheral nervous systems (Robel and Baulieu, 1994). PS and DHEAS are considered as neurosteroids even though its synthesis has not been demonstrated in the brain, since their concentration in brain persists long after removal of gonads and adrenals (Schumacher et al., 1996). Recently, immunohistochemical and biochemical studies revealed the existence of a biosynthetic pathway for neurosteroids within the brain (Akwa et al., 1991; Mellon, 1994; Robel et al., 1995). Cytochrome P450 catalyzed side-chain cleavage (P450_scc) of cholesterol to pregnenolone has been demonstrated in mitochondria of glial cells of brain. Many enzymes involved in the neurosteroid biosynthesis and metabolism are present in both glial cells and neurons (Mellon and Deschepper, 1993; Schumacher et al., 1996), indicating that brain can be a steroidogenic organ and synthesize a variety of neurosteroids.

Multiple lines of evidence suggests that mitochondrial DBI receptors regulate the neurosteroid biosynthesis in neural and extraneuronal tissues (Papadopoulos et al., 1992; Korneyev et al., 1993; Costa et al., 1994a). Activation of mitochondrial DBI receptors facilitates the intramitochondrial flux of cholesterol and thereby increase the availability of cholesterol to the cytochrome P450_scc, an enzyme located in the inner mitochondrial membrane that catalyzes cholesterol side-chain cleavage to yield pregnenolone (Krueger and Papadopoulos, 1992). Activation of mitochondrial DBI receptors by selective agonists such as 4'-
chlordiazepam and FGIN-1-27 (a 3-arylindole-2-acetamide derivative) potently stimulates the neurosteroid biosynthesis in brain (Auta et al., 1993; Korneyev et al., 1993).

The identification of a “steroid binding site” on the GABA-A receptor and its implication in the sedative actions of neuroactive steroids is a landmark discovery (Harrison and Simmonds, 1984; Majewska, 1992; Lambert et al., 1995; Gee et al., 1995). This binding site has been found to be distinctly different from that of benzodiazepine or barbiturate site, respectively (McNeil et al., 1992). The 3α-hydroxy pregnane steroids, AP and THDOC, have been proposed as endogenous ligands of GABA-A receptor complex (Bitran et al., 1991a). Those neurosteroids which are positive allosteric modulators of the GABA-A receptor acting via a unique site on the receptor complex have been termed as "epalons" (Gee et al. 1995). AP and THDOC produce potent barbiturate-like enhancement of GABA-A receptor responses in vitro (Majewska, 1992; Lambert et al., 1995) and induce behavioral sedation when administered in vivo (Belelli et al., 1989; Bitran et al., 1991b). Neurosteroid sulfates PS and DHEAS have been shown to inhibit GABA-A Cl⁻ conductances (Majewska and Schwartz, 1987; Demirgoren et al., 1991). In addition, neurosteroids with partial agonist (5β-THDOC) and inverse agonistic activity (5β-pregnanolone) have been reported (Gee and Lan, 1991; McCauley et al., 1995; Xue et al., 1997). Further, ovarian steroids and neurosteroids profoundly influence the behavioral and neurochemical responses of GABA-A receptor complex (Fernandez-Guasti and Picazo, 1992; Finn and Gee, 1993; 1994; McCauley and Gee, 1995; Bitran et al., 1995).

PS also antagonizes the glycine-activated currents (Wu et al., 1990), enhances the N-methyl-D-aspartate (NMDA)-gated current (Wu et al., 1991) and the NMDA receptor-mediated excitatory responses (Bowlby, 1993) in cultured neurons. DHEAS has been demonstrated to act as positive allosteric modulator at the NMDA receptor complex (Irwin et al., 1994). Neurosteroids pregnenolone, tetrahydrocorticosterone and PS were reported to inhibit the voltage-gated Ca²⁺ channels in isolated neurons (Spence et al., 1991; Ffrench-Mullen et al., 1994).
Recent studies have unfolded that PS competitively inhibit glycine-Cl⁻ channel (Prince and Simmonds, 1992; Wu et al., 1997), while AP allosterically inhibit brain nicotinic receptor (Valera et al., 1992; Bullock et al., 1997).

Several neuroactive steroids, including progesterone, pregnenolone, PS, DHEAS, testosterone and 17β-estradiol, have been shown to inhibit the in vitro binding of the σ receptor radioligands (+)-[^3H]SKF-10,047,[^3H]dextromethorphan and[^3H]haloperidol from rat brain and liver microsomes (Su et al., 1988; Ross, 1991; Yamada et al., 1994). Binding and bioassay studies provided evidence for the existence of at least two subtypes of σ sites, denoted σ₁ and σ₂ (Quirion et al., 1992). A crossed pharmacology between the effects of σ₁ ligands and neurosteroids was recently described; DHEAS and PS behaving as agonists and progesterone as an antagonist (Monnet et al., 1995; Bergeron et al., 1996). Recently, a direct interaction between neurosteroids and σ₁ receptors has been shown by using the in vivo binding assay with the prototypical σ₁ tracer (+)-[^3H]SKF-10,047 (Maurice et al., 1996a). Further, neurosteroids are proposed as endogenous ligands at the central σ receptors, that may constitute a possible mechanism for the neurosteroidal non-genomic effects in behavior and cognition processes.

Although a variety of neurotransmitter systems and ionic channels are sensitive to neurosteroid modulation, the physiological and pharmacological significance of these widespread effects remains unclear. Consistent with their ability to facilitate GABAergic neurotransmission, neurosteroids AP and THDOC produce anaesthetic (Mok et al., 1991), hypnotic (Mendelson et al., 1987), anticonvulsant (Landigren et al., 1987; Hogsikle et al., 1988; Belelli et al., 1989; 1990; Kokate et al., 1994) and anxiolytic (Crawley et al., 1986; Bitran et al., 1991a,b; Weiland et al., 1995) effects. Neurosteroids AP and THDOC have been shown to be potent antistress (Purdy et al., 1991), antiaggressive (Schlega et al., 1985; Kavaliers, 1988), neuroprotective (Frye, 1995) and hyperphagic agents (Chen et al., 1996). A potential role for neurosteroids in ethanol abuse and dependence has also been proposed (Marrow et al., 1996). Ethanol withdrawal...
produces alterations in GABA-A receptors that sensitize to the effects of neuroactive steroids (Devaud et al., 1996), and AP protects against the increased seizure susceptibility associated with ethanol withdrawal (Devaud et al., 1995). Neurosteroid sulfates PS and DHEAS enhanced memory performance in young and aged animals (Flood and Roberts, 1988; Flood et al., 1992; 1995), whereas AP disrupted memory (Mayo et al., 1993). Further, PS and DHEAS produces antiamnestic effects in animal paradigms of learning and memory processes (Itzhak and Alerhand, 1989; Mayo et al., 1993; Cheney et al., 1995a; Meziane et al., 1996; Maurice and Lockhart, 1997).

Normal aging is associated with a decline in cognitive and other brain functions. Apart from the degeneration of cholinergic neurons (Muir, 1997), evidences have suggested that the depression and cognitive dysfunction associated with aging are associated with decreased levels of DHEA and DHEAS (Orentretch et al., 1984; Roberts, 1995). Administration of DHEA and DHEAS improved retention performance in aged animals (Flood and Roberts, 1988), and improved the symptom scoring in patients suffering from depression (Wolkowitz et al., 1997), indicating a pathological role for neurosteroids in brain function. A role for neurosteroids has also been implicated in pathological states such as catamenial epilepsy (Finn and Gee, 1993), stress (Purdy et al., 1991; Owens et al., 1992) and dementia (Nasman et al., 1991).

Several neurosteroids such as AP and its analogs, are unsuitable as therapeutic agents, however, because they are readily oxidized at the 3α-position (Phillipps, 1975), resulting in compounds that are inactive at neuronal but potentially active at hormonal steroid receptors (Gee et al., 1988; Harrison et al., 1987; Hawkinson et al., 1994a; Rupprecht et al., 1993). A 3β-methyl-substituted analog of AP, ganaxolone (CCD 1042) has been recently characterized as a potent anticonvulsant and steroid modulator of GABA-A receptor (Carter et al., 1997). Ganaxolone is currently in phase II clinical trials as neurosteroid-based antiepileptic drug. Another GABA-A receptor active neurosteroid, minaxolone \([2β,3α,5α,11α]-2\text{-ethoxy-3-hydroxy-11-}N,N\text{-dimethyl-amino-pregnane-20-one}\), is
currently under preclinical development (Marshall et al., 1997). However, these agents appear to have the potential of tolerance and dependence liability and other side effects common to GABAergic drugs.

In the light of the above reports, it appears that the family of neurosteroids, including AP, THDOC, progesterone, PS, DHEAS and the mitochondrial DBI receptor ligands 4′-chlordiazepam, PK11195 and FG1N-1-27 are currently being widely used as tool for designing new therapeutic strategies and neurosteroid structure-based drug development. Although neurosteroids have been implicated in aggression, stress, epilepsy, anxiety, sexual and sleep disorders, however, their precise role and mechanism is not yet clear. The neuromodulatory role of neurosteroids in regulating the estrous cycle and pregnancy, memory, and developmental as well as aging processes awaits further investigation. Further, the role of neurosteroids in conditions such as physiological stress, drug addiction, anxiety and feeding behavior, depression and amnesic disorders has received limited attention.

The present thesis work was undertaken to investigate the role of neurosteroids in several psycho-pathophysiological conditions and to elucidate the putative receptor mechanisms involved in the actions of neurosteroids. The work was mainly addressed to six distinct areas of neuropharmacology, viz., stress, anxiety, drug tolerance and addiction, food intake, learning and memory and adrenocorticotropic hormone (ACTH)-induced neuroendocrine behavior. The extensive data generated in the present study has been discussed in six chapters. These studies together with literature support call for the role of neurosteroids and their receptor mechanisms as targets for the developments of new agents with anxiolytic, anticonvulsant, anorectic, antiamnesic and de-addictive properties.