AIMS AND OBJECTIVES

There is a substantial body of evidence linking the role of brain monoamines viz. norepinephrine, serotonin and of late dopamine in the pathophysiology of mental depression. Various classes of antidepressant drugs that are used in the treatment are known to increase the extracellular levels of these neurotransmitters in the brain. The antidepressant drugs included tricyclic antidepressants (TCAs), monoamine oxidase (MAO)-inhibitors, selective serotonin reuptake inhibitors (SSRIs) and the recently available dual or triple reuptake inhibitors. Most patients respond favorably to these pharmacological interventions, however, some do not get complete relief from the symptoms. Changing medications or supplementing with a second medication is helpful for some partial or nonresponders. Therefore, there is always a need for understanding the complete pathophysiology of depression and also to discover newer drugs.

The development of a predictable animal model of mental depression is a great challenge as many of human behavioral symptoms of the disease cannot be reproduced or mimicked in animals. There is a constant need to develop newer animal models and also to validate them.

Out of all the models available, forced swim (FST) and tail-suspension (TST) tests are mainly employed for screening antidepressant drugs. Even though these two behavioral paradigms are extensively used, there have been great strain and situational variability reported in the literature. Therefore, it is essential to support the behavioral observations with in vivo neurochemical and biochemical changes and in vitro receptor or target specificity assays.

With this background, the present study was undertaken to establish and validate these two animal models used to assess antidepressant action(s) of different classes of drugs and to explore neurochemical mechanisms underlying these behavioral paradigms. The study also makes an attempt to investigate some newer targets for
development of newer therapeutic agents for the treatment of depression. In this endeavor, a series of New Molecular Entities (NMEs) were synthesized (in collaboration with the Department of Chemistry, Panjab University, Chandigarh) and were tested. Over all, behavioral, biochemical and neurochemical approaches were the basis of present investigation.

The present study is divided into 8 chapters and each chapter describes the investigations of one or more, but related parameters in the evaluation of the said activity. Chapter 1 deals with the standardization of forced swim and tail-suspension tests using various typical and atypical antidepressants. The validation of both the test procedures has been attempted by calculating the ED50 values and the respective potencies of various classes of antidepressant drugs. Chapter 2 describes the mechanism of action of antidepressant-like effect of bupropion, a dopamine reuptake inhibitor using these behavioral paradigms of despair. Study also correlates the observations with brain neurotransmitter levels. Further, the involvement of L-arginine-nitric oxide-cyclic guanosine monophosphate signaling pathway and the sigma receptor pathway have been elucidated in the antidepressant action. Chapter 3 describes in-depth study of the antidepressant-like effect of venlafaxine, a dual reuptake inhibitor of serotonin and norepinephrine. Further, the involvement of nitric oxide, sigma and alpha-2 adrenergic receptors in its actions has been explored. The studies described in Chapter 4 explore one of the new targets namely neurosteroids in the antidepressant action of drugs. This study describes the antidepressant-like action of dehydroepiandrosterone and pregnenolone sulfate. Chapter 5 describes the role of venlafaxine in chronic fatigue. Various behavioral, biochemical and neurochemical approaches have been made to describe chronic fatigue as well as the role of venlafaxine. Chapter 6, similarly describes the role of dopamine/serotonin/ sigma receptor pathways in the antidepressant-like action of ropinirole, a D2/D3 dopamine receptor agonist. In Chapter 7, a detailed pharmacological profile of one of the herbal molecules, berberine chloride, an alkaloid obtained from Berberis aristata
has been described. A monoaminergic mechanism of action of this herbal compound has been described. One of the main objectives of the research as said earlier, was to discover new drug candidates for antidepressant action. In Chapter 8, a series of New Molecular Entities (NMEs) have been synthesized in collaboration with (Professor S.V. Kessar and his team) the Department of Chemistry of Panjab University, Chandigarh and their pharmacological characterization have been attempted.