INTRODUCTION

The benzodiazepines (BZs) which were introduced in late 1950s into therapeutic practice as 'minor tranquillizers' constitute a novel group of chemical compounds. Among the series of compounds synthesized by Sternbach, chlordiazepoxide was the first BZ to be clinically used, which was followed by now widely used drug, diazepam. Today they (BZs) are the most often prescribed class of psychotropic agents due to their low toxicity, very weak side effects and virtually lack of peripheral effects. The fact that more than 2000 BZ derivatives have been tested and that more than 35 of them are available for human use in different parts of the world indicates the increasing popularity of these drugs as therapeutic agents. This also alarms the possible misuse of these agents. Benzodiazepines have been widely employed...
for the treatment of anxiety and related behavioural disorders, sleep disturbances, status epileptics and other convulsive disorders, and in alcohol withdrawal. They are also used as centrally active muscle relaxants and in anaesthetic practices. Their prescription has now superseded the barbiturates both for sedative, hypnotic, anxiolytic and acute anticonvulsant use.

The mechanism of action of benzodiazepines has been the subject of great interest for neuropsychopharmacologists, neurochemists and clinicians for quite some time. Earlier evidences from behavioural, electrophysiological and biochemical experiments suggested that BZs acted by modulating GABA synaptic function (Costa et al., 1975). Demonstration of specific, saturable, high affinity binding sites for BZs in mammalian brain tissue in recent years was the exciting turning point in BZ research (Squires and Braestrup, 1977). A subsequent study suggested for a strong mutual interaction between GABAergic agents and BZs in binding studies (Gallager et al., 1978; Tallman et al., 1978). These interaction studies and recent advances in the extraction of benzodiazepine receptors from membrane, their solubilization and
chemical analysis, strongly indicated that not only specific benzodiazepine receptors existed but they are also in close physical contact with GABA receptors. The concept of GABA-BZ receptor complex with chloride channel as allosteric regulatory site has thus come into being. The rapid time-course of GABA responses have indicated that GABA receptor is coupled to an ion channel (chloride channel), whose opening and closing is determined by the binding of the effector ligand, neurotransmitter to the regulatory site. Modulation of this postsynaptic GABA-BZ receptor-chloride ionophore complex mediated sedative, anxiolytic anticonvulsant and muscle relaxant actions of benzodiazepines. Many other drugs such as barbiturates also modulated the function of this complex. More recently subtypes of GABA (A and B) have been demonstrated of which subtype A (GABA_A) receptors have been shown to be functionally linked with the central type of BZ receptors (Burch et al., 1982).

In 1981, the first report of a specific BZ receptor antagonist, Ro 15-1788, further supported the view that high affinity BZ binding sites are the recognition sites of specific pharmacological receptors.
that mediated the effects of BZs (Hunkeler et al., 1981). Equally exciting was the discovery of beta-carbolines, which produced effects exactly opposite to that produced by the classical BZ, such as anxiety, convulsion, muscle rigidity and sleep disturbances. These opposing effects were blocked by the BZ receptor antagonist, Ro 15-1788.

The existence of the highly specific BZ binding sites suggests for the presence of possible endogenous ligands. Preliminary data with beta-carbolines were exciting as they were thought to be the candidates since they were isolated from human urine. But it was later found that the beta-carbolines are formed during the extraction procedures with ethanol as solvent. Currently, brain extracts are being screened for a possible endogenous ligand. The diazepam binding inhibiting (DBI) neuropeptide and human endozepine isolated and identified from brain appear to be strong candidates (Marquardt et al., 1986), and the future research will perhaps unravel the physiological functions of these new class of neuropeptides. In the background of these new developments in the area of benzodiazepines, the
present study was undertaken to further explore the interrelationship between GABA-benzodiazepine receptors in terms of physiological functions and drug actions. Special emphasis was laid on investigating the mechanism of withdrawal reaction to diazepam and the possible regulatory role of central alpha$_2$ adrenoceptors in combating the withdrawal reactions. Functional links between benzodiazepine receptors with different subtypes of GABA receptors, purinoceptors, alpha$_2$ adrenoceptors and opiate receptors in modifying stress-induced changes, analgesia, convulsions and other behavioural changes were also investigated.