AIMS AND OBJECTIVES

The present study was designed to investigate the role of central alpha₂ adrenoceptors in the modulation of certain behavioural patterns (e.g. despair behaviour, analgesia, hyperalgesia, abstinence signs etc.) and to assess the potential of clonidine as an investigational tool. The laboratory animals employed in the present study were frogs, albino mice and rats. Clonidine was employed as a prototype alpha₂ agonist and its effects were compared with two other more specific alpha₂ adrenoceptor agonists such as B-HT 920 and guanfacine, which belonged to different chemical classes (Fig 1).

The approach followed to attain this objective is discussed under the following heads, viz.

(i) clonidine-induced behavioural despair: An experimental model to detect the antidepressant activity,

(ii) beta adrenoceptor involvement in forced swimming-induced immobility of mice,

(iii) modification by tricyclic antidepressants of cortical EEG changes induced by
**FIG. 1**

**CLONIDINE**

**B-HT920**

**GUANFACINE**
clonidine in rats, (iv) role of alpha$_2$ adrenoceptors in antinociception, (v) potential of alpha$_2$ adrenoceptor agonists in alcohol abstinence syndrome and (vi) alpha$_2$ adrenoceptor mediated slow and sustained contractions of frog skeletal muscle.

CLONIDINE-INDUCED BEHAVIORAL DESPAIR: AN EXPERIMENTAL MODEL TO DETECT THE ANTIDEPRESSANT ACTIVITY

A great deal of evidence suggests that norepinephrine plays a key role in the pathogenesis of depression (Carlsson et al., 1969; McMillan et al., 1980; Spyraki and Fibiger, 1980). The agents which deplete catecholamines or lower noradrenergic turnover in the brain produce depression-like syndrome in animals. Reserpine-induced behavioural depression may be a result of depletion of both, catecholamines as well as serotonin (Carlsson et al., 1957; Kulkarni and Dandiya, 1975). Recently, it has been shown that in the forced swimming-induced despair test, purine nucleosides prolong the immobility duration of mice probably, by decreasing norepinephrine outflow through their action on presynaptic purinoceptors (Kulkarni and Mehta, 1985). Clonidine, an alpha$_2$ adrenoceptor agonist is reported to produce behavioural depression in several test models. It suppresses operant behaviour (Dwoskin and Sparber,
1983), avoidance behaviour (Kostowski et al., 1981), produces hypothermia (Kulkarni, 1980b), and inhibits exploratory behaviour in laboratory animals (Van der Laan et al., 1985). Therefore, the present investigation was undertaken to investigate the effect of clonidine on forced swimming-induced despair behaviour in mice and its modification, if any, by pretreatment with various antidepressants. The findings were confirmed using two other more specific alpha₂ adrenoceptor agonists, viz. guanfacine (Dausse et al., 1983) and B-HT 920 (Mottram, 1983).

BETA ADRENOCEPTOR INVOLVEMENT IN FORCED SWIMMING-INDUCED IMMOBILITY OF MICE

The neurochemical mechanism for therapeutic action of antidepressant drugs is believed to be the prolongation or potentiation of noradrenergic function (Bunney and Davis, 1965; Schildkraut, 1965). This enhancement in the activity of norepinephrine may be a consequence of inhibition of reuptake process (Iversen, 1974) and/or reduction in the responsiveness of inhibitory alpha₂ adrenoceptors (Pinberg and Tal, 1985). Bergstrom and Kellar (1979) have shown that chronic desmethylimipramine administration selectively decreases the density of beta adrenergic receptors in rat brain. It has also
been speculated that a reduction in $\beta$-adrenoceptor density and desensitization of noradrenergic c-AMP generating systems in the brain, observed after chronic treatment with antidepressants may largely be contributing to their beneficial therapeutic action (Banerjee, et al., 1977; Bergstrom and Kellar, 1979; Vetulani et al., 1976; Wolfe, et al., 1978). Therefore, it appears that central $\beta$-adrenoceptor activation induced by exogenous application of $\beta$-agonists would produce a depression-like syndrome in animals. The present study was designed to explore this possibility by using forced swimming-induced behavioural despair as a test model. Atenolol, metoprolol ($\beta_1$-antagonists), salbutamol ($\beta_2$-agonist) and reserpine (catecholamine depleter) were employed in addition to isoprenaline and propranolol to study the underlying mechanism.

MODIFICATION BY TRICYCLIC ANTIDEPRESSANTS OF CORTICAL EEG CHANGES INDUCED BY CLONIDINE IN RATS

Florio et al., (1975) have demonstrated that the behavioural depression induced by clonidine in rats is accompanied by electroencephalographic (EEG) synchronization. Moreover, antidepressant drugs, particularly when given chronically have been reported to attenuate various effects of clonidine viz. sedation
(Gower and Marriott, 1980), hypothermia (Voigtländer et al., 1978), reduction of norepinephrine turnover (Dubocovich et al., 1979) and suppression of exploratory activity (Kostowski and Malatynska, 1983) in laboratory animals. Hence, it was of interest to study the acute and chronic effects of tricyclic antidepressants on the cortical EEG changes induced by clonidine. Further, it was investigated whether the more specific alpha₂ adrenoceptor agonists such as B-HT 920 (Mottram, 1983) and guanfacine (Dausse et al., 1983) also evoke clonidine-like EEG synchronization or not.

ROLE OF ALPHA₂ ADRENOCEPTORS IN ANTINOCICEPTION

Clonidine, a clinically useful antihypertensive agent, is reported to share many pharmacological characteristics with morphine (Fielding et al., 1978; Kulkarni et al., 1984). For example, both the drugs lower blood pressure (Schmitt et al., 1979), body temperature (Cowan and MacFarland, 1976; Kulkarni, 1980b) and heart rate (De Jonge et al., 1981; Laubie et al., 1979) in laboratory animals. Furthermore, clonidine produces profound antinociception like-morphine when, administered intracerebroventricularray (Schmitt et al., 1974), intrathecally (Reddy et al., 1980)
and systemically (Paalzow, 1974; Luttinger et al., 1985). Although, the involvement of a noradrenergic mechanism in both narcotic analgesia (Cicero et al., 1974; Proudfit and Hammond, 1981) and non-narcotic analgesia (Kulkarni, 1980a; Reddy et al., 1980) has been reported, the analgesic site responsible for the clonidine-induced increase in pain threshold is yet to be identified. In the present study, an attempt has been made to analyse the relative contribution of $\alpha_2$ and opioid receptors, in the antinociceptive effect of clonidine, observed in mice using tail flick technique. The findings were substantiated by determining apparent $pA_2$ values for the underlying antinociceptive site and by recording the effects of clonidine and morphine on cortical EEG in rats.

POTENTIAL OF $\textit{ALPHA}_2$ ADRENOCEPTOR AGONISTS IN ALCOHOL ABSTINENCE SYNDROME

In recent years, alcohol has been identified as a potent and common cause of psychiatric morbidity. More recently, Balldin et al. (1985) have reported that dopamine receptor sensitivity is altered in humans after heavy alcohol intake. Clonidine was found to relieve sweating, tremors and anxiety associated with alcohol withdrawal (Bjorkqvist, 1975).
Since clonidine appears to be an accepted drug for opiate withdrawal (Gold et al., 1978; Washton et al., 1978; Fielding et al., 1978), it was of interest to assess the potential of alpha\(_2\) adrenoceptor agonists in alcohol abstinence syndrome in rats.

**ALPHA\(_2\) ADRENOCEPTOR MEDIATED SLOW AND SUSTAINED CONTRACTIONS OF FROG SKELETAL MUSCLE**

Since the classification of alpha adrenoceptors into alpha\(_1\) and alpha\(_2\) subtypes (Langer, 1974; Starke, 1981), several investigators have attempted to study the nature of these adrenoceptors in various tissue or organ preparations, such as isolated rabbit pulmonary artery (Starke et al., 1975b) rat brain cortex slices (Hedler et al., 1981), dog pulmonary artery (Constantine et al., 1980), rat vas deferens (Drew, 1977b; Hicks et al., 1985), anococcygeus muscle of the rat (Docherry et al., 1979) and rat vascular smooth muscle (Drew and Whiting, 1979; Timmermans and Van Zwieten, 1980). Clonidine was found to provide protection against perphenazine-induced catatonia in rats (Kulkarni, 1981). On the other hand, Pycock et al. (1977) reported that clonidine potentiated the cataleptic action of haloperidol. However, the underlying mechanism (central vs peripheral) for these effects of clonidine
is debatable. Therefore, the present investigation was undertaken to study the *per se* effect of clonidine on frog skeletal muscle and its effect, if any, on acetylcholine-induced contractions. Guanfacine, another alpha_2_ adrenoceptor agonist (Jarrot et al., 1982; Dausse et al., 1983) was employed for comparison.