INTRODUCTION

The rapid and dramatic advances in neuroscience research has revealed a far more complex mechanism of neural signaling which can involve the co-existence of two or more peptide and non-peptide neurotransmitters or neuromodulators. The process of communication between neurons is proving to be much more subtle than originally thought where the interaction of several neuroactive substances with multiple populations of receptors all interact to produce a response.

In the mammalian central nervous system (CNS), the impetus for examining the role of purines as neurotransmitters and/or neuromodulators initially arose from the studies showing that adenosine was a potent stimulator of brain adenylate cyclase activity. However, of more crucial interest was the finding that the methylxanthines, caffeine and theophylline, which were used as cyclic nucleotide phosphodiesterase inhibitors, blocked the actions of adenosine on cyclic AMP formation rather than potentiating them. This led to the hypothesis that the methylxanthines
were adenosine antagonists and that the central stimulant properties of methylxanthines such as caffeine and theophylline might be attributed to the blockade of sedating effects of endogenous adenosine (Sattin and Rall, 1970). Concomitantly, it was suggested in the purinergic nerve hypothesis (Burnstock, 1972), that adenosine triphosphate (ATP), might be the principle neurotransmitter released from the intrinsic, non-adrenergic, non-cholinergic neurons that supply the smooth muscle of intestine and bladder, and possibly some other visceral and vascular organs as well. There is also convincing evidence for purinergic transmission in autonomic ganglia (Akasu et al., 1984), and for purinergic modulation of neurotransmitter release (Stone, 1985; Marangos and Boulenger, 1985; Fredholm and Dunwiddie, 1988).

It is generally accepted that the physiological effects of purine nucleosides and nucleotides might be mediated via discrete cell surface recognition sites or receptors. On the basis of studies related to "nonadrenergic noncholinergic" neurotransmission in peripheral tissues, the purinergic receptors were originally classified as \( P_1 \) and \( P_2 \) purinoceptors (Burnstock, 1978). Responses sensitive to adenosine were attributed to interactions with \( P_1 \) purinoceptors and those sensitive to ATP were suggested to be mediated via \( P_2 \) purinoceptors. \( P_1 \) and \( P_2 \) sites can also be distinguished by the use of selective...
antagonists. For example, methylxanthines such as theophylline and 3-isobutyl-1-methylxanthine, are potent inhibitors of $P_1$ sites but are without effect on $P_2$ sites. Several compounds including quinidine, 2-substituted imidazolamines, 2,2' pyridylisatogen tosylate, were shown to antagonise $P_2$ sites (ATP receptors). However, all of these compounds have nonspecific actions (Burnstock, 1981). Arylaizidoaminopropionyl-ATP (ANAPP$_3$) is claimed as selective $P_2$ purinoceptor antagonist (Hogaboom et al., 1980).

The $P_1$ purinoceptors are further subdivided into $A_1$ (or $R_1$) and $A_2$ (or $R_2$) on the basis of their differential selectivity for a series of adenosine analogs (Van Calker et al., 1979; Londos et al., 1980). The potency series for $A_1$ adenosine receptor mediated responses is $R$-phenylisopropyladenosine ($R$-PIA) = cyclohexyladenosine (CHA) > 5'-N-ethylcarboxamideadenosine (NECA) > $S$-PIA, while the potency series for $A_2$ adenosine receptors is NECA > 2-chloroadenosine (2 CADO) > R-PIA = CHA > $S$-PIA. In most tissues, $A_1$ adenosine receptors mediate inhibition of adenylate cyclase, while $A_2$ adenosine receptors mediate the activation of this enzyme. Adenosine receptors modulate adenylate cyclase activity via G proteins, $G_s$ and $G_i$ for $A_2$ and $A_1$ receptors, respectively (Londos et al., 1983). Optimal activation of these G proteins is dependent on guanine nucleotides such as GTP, $G_p(NH)_p$ or GTP S (Londos et al., 1983; Murayama and Ui, 1983).
In recent years, the concept of different categories of purinoceptors is also emerging. It is suggested that \( P_2 \) purinoceptor may be separated into two subtypes \( P_{2x} \) and \( P_{2y} \) largely on the basis of the rank order of agonist potency of structural analogues of ATP and also on the activity of antagonists at the \( P_2 \)-purinoceptor (Burnstock and Kennedy, 1985). At the \( P_{2x} \) purinoceptor the potency order is \( \alpha, \beta \)-methylene ATP, \( \beta, \gamma \)-methylene ATP, ATP = 2-methylthio ATP. The \( P_{2x} \) purinoceptors are generally excitatory in nature. The responses mediated via \( P_{2x} \) purinoceptors are antagonised by ANAPP\(_3\). Selective desensitization of \( P_{2x} \) purinoceptor can occur by repeated administration of \( \alpha, \beta \)-methylene ATP. The rank order of agonist potency for \( P_{2y} \) purinoceptors is 2 methylthio ATP \( \gg \) ATP \( \gg \) \( \alpha, \beta \)-methylene ATP, \( \beta, \gamma \)-methylene ATP. The \( P_{2y} \) purinoceptor generally mediate relaxation of the smooth muscle. The \( P_{2y} \) purinoceptor mediated effects are weakly antagonised by ANAPP\(_3\) and repeated administration of \( \alpha, \beta \)-methylene ATP can desensitize these receptors (Burnstock and Kennedy, 1985).

Recent electrophysiological studies have, therefore, provided new insights into purinergic mechanisms by suggesting the role of purine nucleotides and nucleosides in neural signaling (Fredholm and Hedqvist, 1980; Burnstock, 1981; Snyder, 1985; Burnstock, 1988). Adenosine is recently suggested to act as an endogenous anticonvulsant (Dragunow, 1986; Dragunow and Robertson, 1987) and
neuroprotective agent (Dragunow and Faull, 1988). Drugs that interact with adenosine receptors have been recently implicated in some neurological diseases of the brain such as epilepsy and stroke (Deckert et al., 1988; Deckert and Gleiter, 1989). It is apparent that the purinergic substances have multitude of effects on physiological function and drug action. However, the presently available experimental evidence on the exact role of purinergic system in physiological functions and pathophysiology of neurological dysfunction as well as psychiatric disorders is far from conclusive. In the light of recent developments in the area of purinergic system, the present study was undertaken to further explore the role of purinergic substances using a simple peripheral model, the anococcygeus muscle preparation and to investigate the possible involvement of purinergic mechanisms in the physiological functions and drug action. Attempts were also made to explore the functional links of purinergic receptors with $\alpha_1$ and $\alpha_2$ adrenoceptors, GABA and benzodiazepine receptors, N-methyl D-aspartate (NMDA) receptors and calcium channels in modifying various behavioural patterns in intact animals and animal tissue preparation.