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EDITORIAL

Prospective role for adenosine and adenosinergic systems in psychiatric disorders[1]

Interest in the role of adenosinergic systems in psychiatric illnesses stems from observations made of caffeine abuse. Chronic excessive consumption of the adenosine receptor antagonist, caffeine, has been reported to induce caffeinism, a syndrome characterized by symptoms of depression, hyperanxiety, increased frequency of psycho-physiological disorders, as well as possible degraded performance (Gilliland & Bullock, 1983). Caffeinism has also been associated with many of the features of anxiety, depression and schizophrenia (Greden, 1974; Greden *et al.* 1978; Lutz, 1978; Mikkelsen, 1978). Additionally, enhanced blood levels of the purines, adenosine and/or adenosine triphosphate have been reported in both schizophrenic and depressed patients (Hansen, 1972) and psychiatric disorders have been noted as symptoms of congenital diseases involving defective purine metabolism (e.g. Lesch-Nyhan syndrome). Recent discoveries have also suggested that existing therapeutic compounds (e.g. carbamazepine and 9-amino-1,2,3,4 tetrahydroacride (THA)) as well as some substances of abuse (e.g. ethanol) and some behavioural therapies (e.g. sleep deprivation and light therapy) may interact with or modulate neuronal adenosine systems: these findings suggest that adenosinergic mechanisms may play a role in a number of psychiatric disorders.

The purine nucleoside, adenosine, fulfils a number of essential metabolic functions, such as a precursor role in the production of adenosine triphosphate (ATP) and other nucleotides. In addition, however, adenosine is also thought to play a key role in neuronal functioning via interactions with specific adenosine receptors, the activation or inactivation of which has been demonstrated to produce profound changes in neuronal functioning (Stone, 1981; Phillis & Wu, 1981*a*, *b*; Dunwiddie 1985; Fredholm & Dunwiddie, 1988).

Neuronal adenosine receptors have been well characterized and at least two distinct sub-types have been identified: adenosine A_1 and A_2 receptors. These receptor subtypes were initially thought to be linked to the enzyme adenylate cyclase, with either a negative (the A_1 receptor) or a positive (the A_2 receptor) coupling influencing the production of the second messenger compound, cyclic adenosine monophosphate (cAMP) (van Calker *et al.* 1979; Londos *et al.* 1979; Bruns, 1980). Subsequently, the rank order of ligand potencies at these receptors has been used as a criterion for characterizing adenosine receptor subtypes, since not all A_1 or A_2 receptors thus characterized appear to be linked to adenylate cyclase (Hamprecht & van Calker, 1985; Fredholm & Dunwiddie, 1988). Pharmacological, physiological and anatomical criteria reveal these two receptor subtypes to be distinct (Stone, 1981; Dunwiddie, 1985) and able to be preferentially radiolabelled (Yeung & Green, 1984). Employing radioligand binding, the relative affinities of adenosine receptor ligands for the A_1 and A_2 receptor sub-types have been well characterized (Bruns *et al.* 1986).

Compounds with selective affinities for adenosine receptors are widely consumed. The methylxanthines caffeine, theophylline and theobromine are present in coffee, tea, cola drinks, cocoa and chocolate, as well as in some common cold medications and appetite suppressant preparations (Gould *et al.* 1984; Uhde 1988). Although these methylxanthines are antagonists at adenosine receptors, they are not particularly potent in terms of their affinity for adenosine receptors; nor do they possess any great selectivity for receptor subtypes. Novel adenosine receptor antagonists have been developed and many of these are much more potent than the existing

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methylxanthines. Some of these have a degree of selectivity for adenosine receptor subtypes (Bruns *et al.* 1986).

Adenosine itself is rapidly metabolized by adenosine deaminase and adenosine kinase and thus direct administration of adenosine is not particularly effective. However, a number of more stable adenosine analogues have been developed which are not readily metabolized. These analogues also vary in their potency and their receptor subtype selectivity (Bruns *et al.* 1986). The receptor subtype selectivity of the existing agonists and antagonists heavily favours the A_1 rather than the A_2 receptor, with relatively few compounds having greater selectivity for the A_2 over the A_1 receptor and those that do, do so only marginally (Bruns *et al.* 1986). A transport system for the re-uptake of released adenosine and other nucleotides is present on the extracellular membranes of many, if not all, cell types. Blockade of this system can increase the receptor availability of adenosine and a number of compounds, such as dipyridamole, nitrobenzylthioinosine, dilazep and mioflazine are thought to achieve their therapeutic effect by inhibiting adenosine uptake (Paterson *et al.* 1981, 1983; Clanachan & Hammond, 1983; Deckert *et al.* 1988). Additionally, inhibitors of adenosine deaminase or adenosine kinase may be effective in raising adenosine levels.

Normal brain concentrations of adenosine have been estimated at about 1–10 micromolar but under conditions of anoxia or hypoxia levels of adenosine can increase dramatically (Berne *et al.* 1974). This, coupled to the general depressant action of adenosine (Phillis *et al.* 1979*a*; Hollins & Stone, 1980), has led to the hypothesis that adenosine plays an important role in activity homeostasis serving as an endogenous neuroprotective compound, playing a role, for example, in limiting or reversing epileptic, ischaemic, anoxic or hypoglycaemic conditions (Dragunow *et al.* 1985; Dragunow & Faull, 1988). Adenosine has also been suggested to play a role in physiological functions such as sleep, respiration and blood pressure (Synder *et al.* 1981; Yarbrough & McGuffin-Clineschmidt, 1981; Dunwiddie & Worth, 1982; Radulovacki *et al.* 1982). Increasingly, adenosine systems have been linked to psychiatric illnesses, either in terms of aetiology or therapeutics (Deckert *et al.* 1988; Williams & Jarvis, 1988; Deckert & Gleiter, 1989). The possible links between adenosinergic mechanisms and disorders, such as anxiety, sleep disorders, psychoses and affective disorders are discussed below. The aim, however, is to heighten awareness of these links rather than to provide a comprehensive review. Additionally, the possible future potential of adenosinergic compounds in psychiatric illness is discussed.

ANXIETY DISORDERS

The adenosine receptor antagonist caffeine produces an anxiogenic profile in experimental animals (File & Hyde, 1979; Pellow *et al.* 1985; Boulenger *et al.* 1986; Lister 1987). In normal humans, caffeine in sufficient doses heightens anxiety (Charney *et al.* 1984; Uhde *et al.* 1984; Loke *et al.* 1985; Boulenger *et al.* 1987), induces increases in blood cortisol levels (Uhde *et al.* 1984) and can potentiate the effects of stress (Cobb, 1974; Lane, 1983). The anxiogenic effect of caffeine is however more pronounced in patients suffering from generalized anxiety disorder (Boulenger & Uhde, 1982) or panic disorder (Boulenger *et al.* 1984; Charney *et al.* 1985; Roy-Byrne & Uhde, 1988). Reductions in anxiety levels can be achieved in some patients by caffeine abstinence alone (Bruce & Lader, 1989).

More indirect evidence for involvement in anxiety comes from adenosinergic modulation of benzodiazepine action (Phillis & Wu, 1982). For example, diazepam can enhance the depressant effects of adenosine (Phillis, 1979). Also, benzodiazepine-induced reductions in neuronal firing rates can be reversed by the adenosine receptor antagonist, theophylline (Phillis *et al.* 1979*b*) and chronic treatment with diazepam desensitizes adenosine A_2 receptors (Hawkins *et al.* 1988*b*, *c*). Additionally, benzodiazepines can inhibit adenosine uptake (Phillis *et al.* 1980; Morgan *et al.* 1983*a*, *b*; Phillis 1984*a*; Morgan & Stone, 1986; Phillis & O'Regan, 1988) and this may influence their anxiolytic profile. Furthermore, both central and peripheral benzodiazepine antagonists and the beta-carboline 'inverse agonists' have adenosine receptor antagonist properties (Phillis & O'Regan, 1987, 1988).

Further evidence for a link between adenosinergic mechanisms and anxiety comes from studies of genetically distinct rat strains. Rats selectively bred for 'emotional reactivity' have significant differences in their adenosine receptor densities; the more emotional Maudsley Reactive strain showing significantly greater adenosine receptor binding sites per unit protein than the less emotional Maudsley Non-Reactive strain (Marangos *et al.* 1987*a*). Interestingly, the same group found no differences between the strains for benzodiazepine binding sites (Tamborska *et al.* 1986) contrary to previous findings (Robertson *et al.* 1978).

There is, however, little behavioural evidence to support an anxiolytic profile for adenosine agonists although they do possess anticonvulsive and sedative actions seen in more accepted anxiolytics, such as benzodiazepines. However, the often marked sedative actions of these compounds may mask any anxiolytic profile in most tests of anxiety. For example, Baldwin & File (1989) report no detectable anxiolytic profile for 2-chloroadenosine, in a social interaction test in rats, but do note significant reductions in motor activity.

SLEEP DISORDERS

Methylxanthine-containing beverages inhibit sleep in humans, both by increasing the latency to sleep and reducing sleep time; the pattern of sleep is also disturbed causing a shortening of the latency to rapid eye movement (REM) sleep (Brezinova *et al.* 1975; Karacan *et al.* 1976; Revelle *et al.* 1980; Dews 1982; Synder & Sklar 1984). However, doses of caffeine below 100 mg (such as those found in tea and cola drinks) may not have significant influences on sleep patterns (Ginsburg & Weintraub, 1976; Dews 1982; Murray, 1988) and tolerance may occur in heavy coffee drinkers (Goldstein & Kaizer, 1969). In rats, caffeine causes increased wakefulness and reductions in total sleep time (both slow wave and REM sleep) (Radulovacki *et al.* 1982; Yanik *et al.* 1987). Also, REM sleep deprivation causes increases in adenosine A_1 receptors (Radulovacki 1985; Yanik & Radulovacki, 1987), an effect which is also seen following chronic caffeine administration (Boulenger *et al.* 1983; Marangos *et al.* 1984; Hawkins *et al.* 1988*a*).

Adenosine agonists induce sedation and have therefore been suggested as possible sleep-enhancing preparations. In experimental animals, the administration of adenosine agonists decreases wakefulness and increases total sleep time, particularly slow wave sleep (Radulovacki *et al.* 1984; Radulovacki, 1985). The analogues used were effective at relatively low concentrations and increasing the dose had no further effect or even diminished the effects. This has been used as evidence that the effects on sleep are mediated via the A_1 receptor, since the analogues are relatively more selective for this receptor (compared to the A_2 receptor) in this dose range; this is of interest since the hypomobilizing effects of adenosine analogues appears to be mediated by the A_2 rather than A_1 receptors (Spealman & Coffin, 1986; Durcan & Morgan 1989*a*, *b*). These compounds, unlike other sleep-inducing agents such as the benzodiazepines and barbiturates, do not reduce REM sleep and if anything enhance it (Radulovacki *et al.* 1984). In addition to adenosine analogues, S-adenosyl-L-homocysteine, which is broken down to adenosine and homocysteine, also enhances sleep (Sarda *et al.* 1989) as does deoxycoformycin, an adenosine deaminase inhibitor (Radulovacki *et al.* 1983; Virus *et al.* 1983). The adenosine transport inhibitor, mioflazine, also enhances sleep patterns in dogs and this effect can be antagonized by caffeine (Wauquier *et al.* 1987). The effects of mioflazine on sleep in rats were only apparent during the light phase of the circadian cycle (when the rats would normally sleep); this is of interest in light of reports of circadian variation in adenosine receptor density (Virus *et al.* 1984). Mioflazine is also reported to be an effective sleep promoter in human subjects suffering from sleep disturbance and compares well with the benzodiazepine, flunitrazepam (Hoppenbrouwers & Vanden Bussche 1989).

DISORDERS OF ATTENTION AND COGNITION

In normal subjects of all ages caffeine has been demonstrated repeatedly to increase attention, vigilance, and cognitive functioning (Elkins *et al.* 1981; Rapoport *et al.* 1981; Lieberman *et al.* 1987;

Pons *et al.* 1988; Swift & Tiplady, 1988) and has been reported effective in increasing performance and decreasing lapses of attention in hyperkinetic children (Reichard & Elder, 1977; Harvey & Marsh, 1978). However, at least some hyperactive children respond to sympathomimetics to a greater extent than to caffeine (Conners, 1979). In this respect caffeine may bring about its therapeutic action by modulating monoamine neurotransmission, which has been extensively documented in studies performed *in vitro* (Fredholm, 1976; Clanachan *et al.* 1977; Harms *et al.* 1979; Michaelis *et al.* 1979).

One of the most promising therapeutic compounds in the treatment of Alzheimer's disease is the anticholinesterase compound 9-amino-1,2,3,4-tetrahydroacridine (THA), which has been reported to improve memory dramatically in Alzheimer's dementia (Summers *et al.* 1981, 1986). Consensus opinion is that THA may largely act by inhibiting cholinesterases (Drukarch *et al.* 1987; Nilsson *et al.* 1987). An anticholinesterase action of THA does not, however, seem likely to be a complete explanation of its effectiveness in Alzheimer's dementia, since THA is far more effective in treating Alzheimer's dementia than other anticholinesterases, suggesting that additional mechanisms may be involved in its therapeutic efficacy (Reiner & McGeer, 1988); other studies suggest that THA may modulate neuronal levels of not only acetylcholine but also monoamines (Drukarch *et al.* 1988; Reiner & McGeer, 1988). THA has also been reported recently to interact with adenosinergic systems and adenosine A_1 receptors. For example, *in vitro* studies of the inotropic effects of adenosine and 2-chloroadenosine reveal that 1–4 micromolar THA reversed the negative inotropic effects of these adenosinergic compounds and THA has also been demonstrated to be a weak competitor at adenosine A_1 receptors in guinea-pig brain (Freeman *et al.* 1988). Since *in vitro* studies reveal that adenosine and some of its more stable analogues can inhibit the release of acetylcholine and monoamines from neuronal preparations (Ginsborg & Hirst, 1972; Harms *et al.* 1978, 1979; Michaelis *et al.* 1979), inhibition of adenosinergic modulation of acetylcholine or monoamine neurotransmitter release may play a role in the clinical effectiveness of THA in Alzheimer's dementias.

PSYCHOTIC DISORDERS

An antipsychotic potential for adenosine agonists may be indicated, in part, on the basis of the regional distribution of adenosine receptors. While A_1 receptors are located in many brain areas, the A_2 subtype are largely restricted to dopamine-rich regions, such as the caudate putamen, nucleus accumbens and the olfactory tubercle (Premont *et al.* 1979; Bruns *et al.* 1980, 1986; Wojcik & Neff, 1983*a*, *b*). This has led to speculation that adenosinergic compounds may have antipsychotic potential, possibly as a consequence of modulation of dopamine release (Myers & Pugsley, 1986), since these brain areas have also been implicated in antipsychotic drug action.

In vitro studies reveal that adenosine or its analogues can inhibit dopamine release (Harms *et al.* 1979; Michaelis *et al.* 1979) and desensitize dopamine receptors (Porter *et al.* 1988). Administration of adenosine analogues *in vivo* has been shown to influence dopamine metabolism in this region (Dunwiddie, 1985; Myers & Pugsley, 1986) and bilateral injections of these analogues directly into the striatum are reported to depress locomotor activity (Barraco & Bryant, 1987). Adenosine agonists also alter behaviours which are thought to be mediated by dopaminergic mechanisms and have been used as models of antipsychotic activity; for example, the inhibition of locomotor activity (Synder *et al.* 1981; Phillis *et al.* 1986; Durcan & Morgan 1989*a*, *b*), ataxia (Geyer *et al.* 1982; Heffner *et al.* 1985), Sidman avoidance responding (Bridges *et al.* 1987) apomorphine-induced rotational behaviour (Fredholm *et al.* 1984) and the enhancement of prolactin release (Stewart & Pugsley, 1985). The adenosine agonist, N^6-(2,2-diphenylethyl)adenosine, compares favourably with haloperidol and thioridazine on these tests (Bridges *et al.* 1987). The adenosine receptor antagonist theophylline (in the form of aminophylline) blocks adenosine agonist-induced increases in prolactin release (Stewart & Pugsley, 1985); theophylline, and its analogue 8-phenyl theophylline, both potentiate apomorphine-induced rotational behaviour (Fredholm *et al.* 1984). Additional evidence comes from reports that the neuroleptic compound, haloperidol, potentiates the R-phenylisopro-

pyladenosine (R-PIA)-induced increase in prolactin secretion (Stewart & Pugsley, 1985) whereas methylxanthine-containing beverages antagonize the behavioural effects of haloperidol (Foussard-Blanpin & Barbier, 1986). The adenosine receptor subtype involved in the modulation of dopamine release remains to be clarified; however, it would appear that compounds with higher affinities to the A_2 receptors as compared to A_1 receptors are more potent in suppressing behavioural phenomena related to dopaminergic activity, such as locomotor activity (Barraco & Bryant, 1987; Durcan & Morgan 1989*a*, *b*).

The modulation of dopamine release not only suggests a role for adenosine agonists in antipsychotic therapy by inhibiting dopamine release, but also suggests that adenosine antagonists may be useful in movement disorders such as Parkinson's disease and tardive dyskinesia by virtue of their enhancement of dopamine release (Fuxe & Ungerstedt, 1974).

LESCH-NYHAN SYNDROME

Lesch-Nyhan syndrome (Lesch & Nyhan, 1964), which appears to result from a deficiency of the purine salvage mechanism, involving a defect in the gene encoding the enzyme hypoxanthine-guanine phosphoribosyl transferase, also appears to be associated with changes in CNS monoamine turnover (Baumeister & Frye, 1985). Thus, studies of CSF composition in Lesch-Nyhan boys reveal marked reductions in the levels of homovanillic acid and 3-methoxy-4-hydroxy-phenylethylene glycol and high levels of 5-hydroxyindoleacetic acid in CSF suggesting reduced dopamine and noradrenaline turnover and increased serotonin turnover (Jankovic *et al.* 1988). Neonatal lesioning of dopamine neurons with 6-hydroxy-dopamine in rats has been proposed as an animal model of the dopamine deficiency in Lesch-Nyhan syndrome (Breese *et al.* 1984). Such animals, which exhibit nucleoside and nucleotide levels within the normal range, have been reported to be supersensitive to the adenosine antagonist, theophylline (Criswell *et al.* 1988). Additionally, chronic administration of high doses of methylxanthines can induce self-injurious behaviour in rodents (Peters, 1967; Sakata & Fuchimoto, 1973; Lloyd & Stone, 1981). The adenosine agonists N-ethyl carboxamido-adenosine (NECA) or 2-chloroadenosine are reported to block l-dopa or SKF 38393 (a direct acting D_1-dopamine agonist)-induced self-mutilation in this animal model (with relative A_1 and A_2 adenosine receptor potencies suggesting an adenosine A_2-mediated action) (Criswell *et al.* 1988). Such data would suggest that adenosine agonists, and A_2 agonists such as NECA in particular, may be useful in ameliorating dopamine-mediated symptoms of Lesch-Nyhan syndrome.

BIPOLAR AFFECTIVE DISORDERS

A possible role for adenosine in bipolar affective disorders comes largely from circumstantial evidence linking adenosinergic mechanisms to some of the treatment strategies, such as electroconvulsive shock, sleep deprivation, lithium and tricyclic drug administration. Antidepressant drugs are reported to increase cyclic AMP via adenosinergic mechanisms (Sattin *et al.* 1978; Sattin 1981*a*, *b*), whereas lithium is reported to inhibit adenosine-induced increases in cyclic AMP (Ebstein *et al.* 1978; Hamburger-Bar *et al.* 1986). Electro-convulsive shock (ECS) increases A_1 receptors (Newman *et al.* 1984; Gleiter *et al.* 1989), although these changes are not accompanied by any changes in seizure threshold to caffeine (Gleiter *et al.* 1988); REM sleep deprivation also increases A_1 receptors (Radulovacki, 1985). However, carbamazepine treatment is the most extensively investigated in relation to adenosine.

Carbamazepine (Tegretol) has a number of clinical actions including antidepressant and antimanic properties (Ballenger & Post, 1980; Post *et al.* 1984; Stromgren & Boller, 1985; Ballenger, 1988; Botte & Charles, 1988) and these may be superior to other treatments for certain sub-populations of depressive patients (e.g. rapid cycling illnesses (Post, 1989)). Although it possesses a primary tricyclic chemical structure, carbamazepine is reported to bind competitively to neuronal adenosine receptors both in rodent (Skerritt *et al.* 1982, 1983; Weir *et al.* 1984; Fujiwara *et al.* 1986; Marangos *et al.* 1987*c*) and in human post-mortem (Dodd *et al.* 1986) brain membranes, possibly binding

largely to the adenosine A_1 receptor (Weir *et al.* 1984; Clark & Post, 1989). It has been suggested that interactions at adenosine receptors may contribute to, or even underlie, the therapeutic efficacy of carbamazepine (Skerritt *et al.* 1982, 1983; Hood *et al.* 1983; Weir *et al.* 1984; Fujiwara *et al.* 1986; Dodd *et al.* 1986; Marangos *et al.* 1987*b*). The principal rationale for this assertion is that carbamazepine inhibits *in vitro* ligand binding to adenosine receptors at concentrations within the therapeutically effective plasma concentration range (Skerritt *et al.* 1982, 1983), although it should be pointed out that these *in vitro* binding studies are conducted at ambient temperatures considerably below body temperature and may not reflect *in vivo* affinities or binding characteristics. Furthermore, drug interaction, thermodynamic and chronic drug treatment studies of the effect of carbamazepine on adenosine ligand binding have been interpreted as revealing antagonist properties for carbamazepine (Skerritt *et al.* 1983; Marangos *et al.* 1987*b*, *c*; Daval *et al.* 1989), a contention that is supported by *in vivo* microiontophoretic studies of neuronal firing rate in rat brain (Phillis, 1984*b*). If adenosine receptors figure largely in the therapeutic efficacy of carbamazepine, then adenosine antagonism is a somewhat surprising efficacy, since it also possesses potent anticonvulsant properties (Skerritt *et al.* 1982, 1983; Weir *et al.* 984), while many other adenosine receptor antagonists exhibit convulsant activity (Richie, 1975; Morgan *et al.* 1989) and adenosine itself potently depresses neuronal activity (Hollins & Stone, 1980; Stone, 1981; Phillis *et al.* 1979*a*). Also, the adenosine antagonists caffeine and theophylline, at high but sub-convulsive doses, do not alter the anticonvulsant potency of carbamazepine on amygdala-kindled seizures (Weiss *et al.* 1985) nor do they appear effective in affective disorders, in fact, high doses of caffeine have been reported to exacerbate depressive mood (Veleber & Templer, 1984). Further investigations are required to determine the role of adenosine receptors in the therapeutic efficacy of carbamazepine.

ALCOHOL AND DRUG ABUSE

Investigations of interactions of adenosinergic compounds with the behavioural effects of ethanol have focused largely on methylxanthine adenosine receptor antagonists. Ethanol does not appear to affect adenosine levels *per se* (Phillis *et al.* 1980*b*; Clark & Dar 1988*a*); however, ethanol administration does cause an increase in A_1 adenosine receptor binding sites (Dar *et al.* 1983; Clark & Dar, 1988*b*), thus suggesting that it is sensitivity to adenosine or adenosinergic drugs, rather than changes in adenosine levels, which may account for the reported interactions with ethanol.

Ethanol administration causes a number of physiological and behavioural effects and some, but not all, of these can be attenuated by adenosine antagonists (Dar *et al.* 1983; 1987; Clark & Dar, 1988*b*; Dar, 1988; Dar & Wooles, 1988; Hilakivi *et al.* 1989). Adenosine receptor agonists such as N^6 R-phenylisopropyladenosine (R-PIA) and uptake blockers such as dipyridamole and dilazep have been conversely reported to potentiate the sedative and motor incoordinating effects of ethanol (Dar *et al.* 1983; Clark & Dar, 1988*b*). Further evidence for a link between the effects of ethanol and adenosinergic mechanisms comes from reports that mice selectively bred for sensitivity to ethanol show differential behavioural sensitivity to adenosinergic drugs (Proctor & Dunwiddie, 1984; Fredholm *et al.* 1985; Proctor *et al.* 1985) and differences in numbers of adenosine A_1 receptors (Fredholm *et al.* 1985).

Human studies have not provided any clear indication as to the ethanol antagonizing properties of methylxanthines despite the widespread belief in the sobering properties of coffee. These studies have suffered from problems of prior experiences with ethanol or methylxanthine-containing beverages, the doses of each of the drugs used, intervals between their administration, and the types of test used. Some studies have suggested that caffeine can antagonize some, but not all ethanol-induced impairments (Forney & Hughes, 1965; Franks *et al.* 1975; Linnoila & Mattila, 1981) while others have found no significant antagonistic effect (Newman & Newman, 1956; Oborne & Rodgers, 1983). There is little evidence to support the notion of an amethystine effect of caffeine (Nash, 1966; Fubin & Nicastro, 1988). Post-ethanol administration of aminophylline (which breaks down to theophylline and ethylenediamine) has also been shown to reduce ethanol's effects on the

EEG and motor coordination (Alkana *et al.* 1977); however, the ethylenediamine (a structural analogue of GABA) may be playing a role in these effects.

Adenosinergic mechanisms may also be implicated in opiate dependence. Methylxanthines can reverse some of the acute effects of opiates (Ho *et al.* 1973; Stone & Perkins, 1979; Perkins & Stone, 1980; Ahlijanian & Takemori, 1985) and can precipitate withdrawal signs in morphine-dependent rhesus monkeys (Aceto *et al.* 1978). The effects of methylxanthines on the development of morphine tolerance and dependence is, however, less clear with reports of both increases (Ho *et al.* 1975; Francis *et al.* 1976; Hammond *et al.* 1976) or decreases (Matsuda, 1970; Brailowsky *et al.* 1981; Ahlijanian & Takemori, 1986*a*). Morphine tolerant or dependent mice are also reported to be more sensitive to drugs acting at adenosine receptors (Ahlijanian & Takemori, 1986*b*).

PSYCHIATRIC POTENTIAL OF ADENOSINERGIC DRUGS

It is clear from the above discussion that the modulation of adenosinergic systems may play a role in the treatment of a number of psychiatric disorders. However, it is equally clear that the evidence is, in many instances, largely circumstantial and in some cases rather circular. While drugs acting on adenosinergic mechanisms provide no 'magic bullets', they may, as a consequence of adenosine's modulatory action on neuro-transmitter systems, provide some therapeutic potential either directly or adjunctively with other treatment modalities.

Existing adenosine receptor agonists and antagonists are, however, unlikely to be of major use in psychiatric disorders. For example, known adenosine agonists are potent hypotensive agents (Vapaatalo *et al.* 1975; Phillis & Wu, 1981*b*; Berne *et al.* 1983) and produce marked sedation (Dunwiddie & Worth, 1982; Phillis *et al.* 1986) and bradycardia (Barraco *et al.* 1984, 1986), as well as proconvulsant actions (Morgan *et al.* 1989). Conversely, side effects of antagonists, such as convulsant properties (Richie, 1975) and tachycardia (Belardinelli *et al.* 1983), equally detract from therapeutic usefulness. Such adverse actions may not be insuperable: adenosine receptors are heterogeneous, with at least two receptor sub-types currently established (Stone, 1981; Dunwiddie, 1985). At present only very A_1 receptor subtype selective compounds have been developed; very A_2 selective compounds may well be developed in the near future. Additionally, other adenosine receptor subtypes may be uncovered, for example, an adenosine A_3 receptor has been proposed (Riberio & Sebastiao, 1986). Compounds which have greater selectivity for non-A_1 receptor subtypes may possess fewer adverse side effects and thus cause a reappraisal of the role of adenosinergic systems in psychiatric disorders. In particular, the fact that adenosinergic systems are capable of inhibiting the release of a wide array of neurotransmitters (Dunwiddie, 1985; Fredholm & Dunwiddie, 1988) suggests that adenosinergic systems may modulate a common excitation-coupled release mechanism. Although this might appear a very non-specific action, the very discrete distribution of adenosine A_2 receptors (largely in the striatum) may give A_2 receptor selective ligands localized actions; this may be especially relevant in the treatment of illnesses associated with disruptions of the nigro-striatal axis.

Of the treatment modalities at present in use which have been demonstrated to interact with adenosine receptors (such as carbamazepine, tetrahydroacride, or ECT) there is no strong evidence to suggest that adenosinergic modulation is a primary action. The main problem here is that little is known about the therapeutically important mode of action of these treatments. The major role of existing adenosinergic compounds in psychiatric disorders may be in further delineating brain mechanisms associated with those disorders. Their use as pharmacological tools may be extremely important in elucidating the action of currently employed treatments. They may also point the way to more effective pharmaceutical treatment modalities involving either adenosinergic or non-adenosinergic mechanisms.

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