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Potentiation of the action of adenosine on cerebral cortical neurones by the tricyclic antidepressants

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1 The effects of four tricyclic antidepressants, nortriptyline, iprindole, chlorimipramine and desipramine on adenosine-evoked depressions of the firings of rat cerebral cortical neurones has been studied.

2 When applied iontophoretically, all four substances enhanced the depressant actions of iontophoretically applied adenosine but did not affect the depressant actions of the uptake-resistant analogue, adenosine 5'-N-ethylcarboxamide (NECA).

3 Nortriptyline and iprindole administered intravenously (1 mg kg^{-1}) enhanced the depressant actions of iontophoretically applied adenosine.

4 When applied by larger iontophoretic currents, all four antidepressants inhibited the firing of cerebral cortical neurones. Chlorimipramine- and desimipramine-elicited depressions were antagonized by intravenously administered caffeine, an adenosine antagonist.

5 Earlier studies showed the tricyclic antidepressants inhibit the uptake of adenosine by rat brain cerebral cortical synaptosomes. The present results demonstrate that four antidepressants are able to potentiate the action of adenosine and that this occurs when these compounds are given in behaviourally meaningful doses. The specificity of the potentiation is demonstrated by the failure of these compounds to potentiate the depressant actions of an uptake-resistant analogue of adenosine, NECA.

6 Antagonism of the inhibitory effects of the antidepressants on neuronal firings by caffeine, indicates that these compounds can enhance the extracellular levels of endogenously released adenosine sufficiently to depress cell firing.

Introduction

Adenosine and the adenine nucleotides depress the activity of central neurones *in vivo* (Phillis *et al.*, 1979). Purines are released from central tissues during stimulation (Sulakhe & Phillis, 1975; Jhamandas & Dumbrille, 1980) and adenosine has been shown to inhibit the release of several neurotransmitters from brain tissues as a result of its suppression of calcium fluxes into the nerve terminal (Phillis & Wu, 1981). In behavioural tests, adenosine and its derivatives have been shown to have sedative, hypnotic and anticonvulsant activity (Dunwiddie & Worth, 1982; Radulovacki *et al.*, 1982; Barraco *et al.*, 1983; 1984; Coffin *et al.*, 1984). Inhibitors of adenosine uptake such as nitrobenzylthioinosine and papaverine depress locomotor activity in mice (Crawley *et al.*, 1983; Coffin *et al.*, 1984). The adenosine antagonist, caffeine, has behaviourally stimulant and proconvulsant actions (Phillis & Wu, 1981).

In the light of these actions it has been proposed that adenosine acts as a modulator of synaptic transmission in the central nervous system (Phillis & Kostopoulos, 1975; Phillis & Wu, 1981) and it has been proposed that a number of centrally acting drugs could exert their effects by purine-mediated mechanisms (Phillis & Wu, 1981; 1982a,b).

The tricyclic antidepressants are effective therapeutic agents for various forms of affective psychoses. Their mechanisms of therapeutic action have, however, remained somewhat obscure because almost all specific pharmacological actions in experimental animals have been reported on the basis of single, acute treatments while therapeutic antidepressant actions require prolonged treatments of a week or more. Recent observations of the adaptive changes in adrenoceptor properties in chronically treated animals have provided some potential insights into the fundamental actions of the tricyclic antidepressants underlying their therapeutic effects.

Chronic treatment with imipramine or desipramine reduced the sensitivity of cortical (Schultz, 1976) and mesolimbic (Vetulani & Sulser, 1975) adenylate cyclase to noradrenaline.

On acute administration, the tricyclic antidepressants possess central depressant activity in normal animals. They reduce spontaneous motor activity, induce sedation, increase electroencephalographic and behavioural arousal thresholds and exert anticonvulsant effects (Moller-Nielsen, 1980; Gogolák, 1980). The mechanisms by which the antidepressants exert such central depressant activity upon acute administration have not been clarified and are probably only indirectly related to their therapeutic activity as antidepressants.

An involvement of adenosine in the actions of the tricyclic antidepressants was suggested by the finding that these agents inhibit the uptake of adenosine by rat brain cortical synaptosomes (Phillis & Wu, 1982a,b). Inhibition of adenosine uptake can explain the enhanced release of labelled purine from guinea-pig cortical slices by desipramine (30–500 μM) (Pull & McIlwain, 1976; Sattin, 1981) and the theophylline-antagonized increase in cyclic AMP accumulation in guinea-pig cortical tissues by a number of antidepressants (Kodama *et al.*, 1971; Huang & Daly, 1974; Sattin *et al.*, 1978). Although these effects required concentrations in the 10^{-4} M range, which are considerably higher than the 1 μM plasma levels typical of chronically treated patients, a number of animal and human studies have shown that the lipophilicity of these drugs can result in brain levels 10–40 times higher than plasma levels (Jori *et al.*, 1971; Biegon & Samuel, 1979; Hrdina & Dubas, 1981; Kristinsson *et al.*, 1983; Bickel *et al.*, 1983). Thus brain levels in animals and patients treated with the tricyclic antidepressants could achieve the levels necessary for inhibition of adenosine uptake and enhancement of cyclic AMP formation.

Potentiation of the depressant actions of adenosine on the firing of rat cerebral cortical neurones by iontophoretically applied antidepressant drugs has been described (Sattin *et al.*, 1978; Stone & Taylor, 1979). The present paper confirms these observations and demonstrates that systemically administered antidepressants, in similar doses to those used in behavioural experiments, also enhance the depressant effects of adenosine. The antidepressant drugs, themselves, were able to inhibit the firing of cortical neurones and these effects could be antagonized by caffeine, suggesting that these agents are able to enhance extracellular levels of endogenously released adenosine sufficiently to affect cell firing. The findings support the suggestions that adenosine is implicated in the central actions of the tricyclic antidepressants.

Methods

The experiments described here were conducted on 35 adult male Sprague-Dawley rats (350–375 g body weight). The animals were anaesthetized with halothane, and, after insertion of a tracheal cannula, anaesthesia was maintained with a mixture of methoxyflurane, nitrous oxide (75%) and oxygen (25%). The animals were placed in a stereotaxic frame and body temperature was maintained at 37°C via an electric heating pad controlled by a rectal thermal probe. After reflection of the skin overlying the dorsal skull, a small hole was drilled through the parietal bone 2 mm lateral to the sagittal suture and 1.5 mm posterior to the coronal suture line. This hole allowed access to the sensorimotor cortex after a slit had been made in the dura mater. The exposed skin, muscle and bone were covered with a thin layer of 4% agar in Ringer solution to prevent drying and to stabilize the cortical surface. A cannula was inserted into the left femoral vein for intravenous injections.

Seven barrelled micropipettes were used to record extracellular action potentials and apply drugs by iontophoresis or electro-osmosis onto cerebral cortical neurones. The central recording barrel and one side barrel were filled with 2 M NaCl and the remaining barrels were filled by centrifugation with various combinations of the following substances: adenosine hemisulphate (0.1 M, pH 4.0), acetylcholine chloride (0.1 M, pH 5.0), adenosine-5′-*N*-ethylcarboxamide (0.01 M, pH 6.0, a gift of the Warner-Lambert Co.), nortriptyline hydrochloride (0.05 M, in 50 mM NaCl, pH 5.2), chlorimipramine hydrochloride (0.05 M, in 50 mM NaCl, pH 5.0), iprindole hydrochloride (0.05 M, in 50 mM NaCl, pH 4.6), desipramine hydrochloride (0.05 M in 50 mM NaCl, pH 5.8). Substances were tested on deep (1000–1400 μm) spontaneously firing, acetylcholine excited, neurones in the sensorimotor cortex. Earlier studies have shown that most of these neurones can be identified as corticospinal cells (Phillis *et al.*, 1979). Drug effects were evaluated by observing changes in the rate of spontaneous firing or by monitoring their effects on the depressant action of adenosine.

Adenosine was applied repetitively by 15–20 s pulses of current generated by a Dagan polarizer at interpulse intervals of between 90 and 120 s. When the responses to adenosine had stabilized, an antidepressant was applied concurrently for periods of up to 8 min. The durations of the depressions of spontaneous firing elicited by three pre-antidepressant applications of adenosine were measured from the onset of application to the point at which firing recovered to control levels. These were compared with those of three consecutive adenosine responses immediately following the application of

the antidepressant agent. Adenosine applications were continued until the duration of the depressions had recovered to control values. Control studies have shown that the responses to pulsed adenosine remain constant for prolonged periods (up to several hours in some instances). The antidepressants tested had depressant actions on the firing of cerebral cortical neurones. Therefore, in the present studies with adenosine, the antidepressants were also tested in the absence of adenosine application to ensure that the amounts applied were insufficient to depress neuronal firing.

In several instances, the antidepressants nortryptiline and iprindole were administered intravenously and their effects on the duration of iontophoretically applied adenosine evoked depressions were ascertained.

Results

Nortriptyline

The spontaneous electrical activity of cerebral cortical neurones was recorded before, during and after the iontophoretic application of nortriptyline. When applied with sufficiently large currents, nortriptyline depressed the spontaneous and acetylcholine-evoked firing cortical neurones. The depressions were relatively slow in onset, taking several minutes to develop and recoveries were prolonged over 20–40 min. For tests of its interaction with adenosine-evoked depressions, the nortriptyline application currents were adjusted to have a minimal effect on spontaneous firing rates.

Adenosine depresses the spontaneous firing of cerebral cortical neurones. Once the responses to adenosine had stabilized, nortriptyline was applied concurrently and the changes in the magnitude and duration of the adenosine-evoked inhibition observed. An example of the testing sequence is shown in Figure 1. Adenosine (31 nA) depressed the spontaneous firing of this neurone. Nortriptyline (5 nA) was then applied for 3 min. During this period of time, the responses to adenosine were enhanced in magnitude and duration to the extent that the neurone virtually ceased to fire for nearly 4–5 min. Spontaneous activity then gradually recovered and had returned to control levels 10 min after the nortriptyline application. The responses to adenosine were still potentiated in magnitude and duration and full recovery did not occur for a further 20 min. Adenosine applications were then discontinued and nortriptyline (5 nA) applied again (Figure 1b). With this application current it slightly enhanced the firing of the cell, establishing that the depression observed during the initial trial was due to a very pronounced

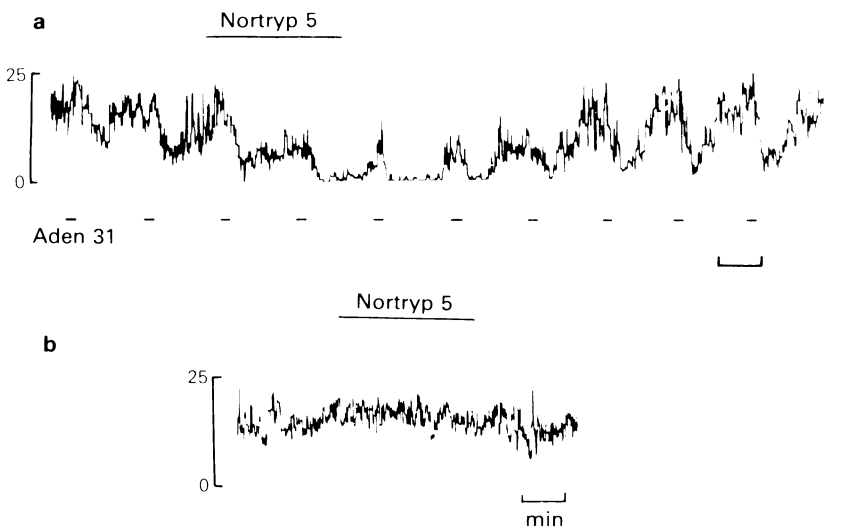

Figure 1 Firing frequency records of a spontaneously firing rat cerebral cortical neurone. This is a rate meter recording with the number of action potentials per second on the ordinate scale. Horizontal bars above and below the records indicate periods of drug application. (a) Adenosine (Aden, 31 nA) reduced the rate of firing during and after the application of nortriptyline (Nortryp, 5 nA) the effects of adenosine were greatly potentiated, to the point where firing was nearly abolished. Recovery occurred slowly over a period of 30 min. (b) Shows the lack of effect of a second administration of nortriptyline (5 nA) on the spontaneous firing of this neurone when the adenosine pulses were discontinued.

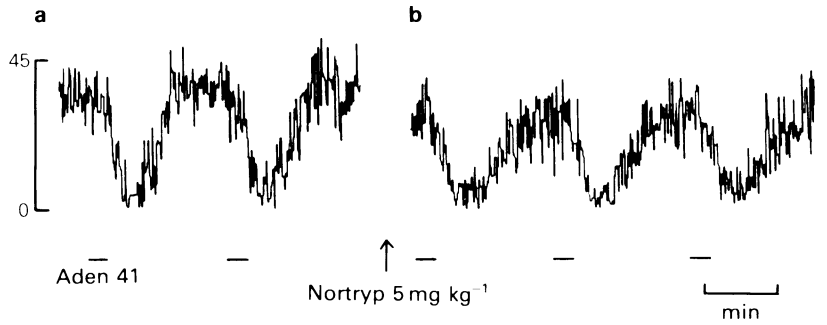

Figure 2 Responses to adenosine (Aden 41 nA) pulses before (a) and 12–18 min after the intravenous administration of nortriptyline (Nortryp, 1 + 4 mg kg^{-1}).

potentiation of adenosine.

Adenosine and nortriptyline were tested on 35 neurones in four animals. Potentiation of the adenosine response was observed in every instance, the duration of the purine-evoked responses being increased by between 8 and 61%. For these neurones, the mean duration of the adenosine-evoked controls was 65.8 ± 1.1 (s.e.mean). Immediately following the application of nortriptyline, the duration of the adenosine responses was 81.6 ± 1.4 s, a mean increase in duration of 15.8 s ($P < 0.001$).

A feature of the potentiating effects of the antidepressants was the relatively slow time course of the effect. Thus potentiation developed over a period of 2–5 min after ending the drug application, with recovery occurring with an even slower time course.

Nortriptyline also potentiated the depressant effects of adenosine when tested on 8 neurones in 8 rats by intravenous administration in doses of 1 and then 4 mg kg^{-1}. At the 1 mg kg^{-1} dose level there was no effect on neuronal firing rates, but when the subsequent dose of 4 mg kg^{-1} was administered 20–25 min later, a small reduction in spontaneous firing was observed. This is evident in Figure 2 where the records in Figure 2b, obtained 12–18 min after the second dose of nortriptyline, illustrate both the small reduction in the rate of spontaneous firing and the enhanced duration of the adenosine elicited inhibitions.

The control adenosine depressions of the 8 tested neurones had a mean duration of 71.1 ± 2.0 s. When tested 10–16 min after the administration of nortriptyline (1 mg kg^{-1}) intravenously, the duration of the adenosine responses was significantly enhanced (85.4 ± 4.9 s; $P < 0.05$). The second injection of nortriptyline (4 mg kg^{-1}) resulted in an even greater potentiation of the responses to adenosine (92.8–3.4 s; $P < 0.001$).

Iprindole

Iprindole, applied iontophoretically in amounts that do not directly depress spontaneous firing, was tested on 27 cerebral cortical neurones; it potentiated the effects of adenosine on 24 of these. The mean duration of the adenosine-evoked control depressions was 68.0 ± 1.9 s. Immediately after the application of iprindole the duration of the adenosine response for all 27 neurones was increased to 80.4 ± 1.6 s, a mean

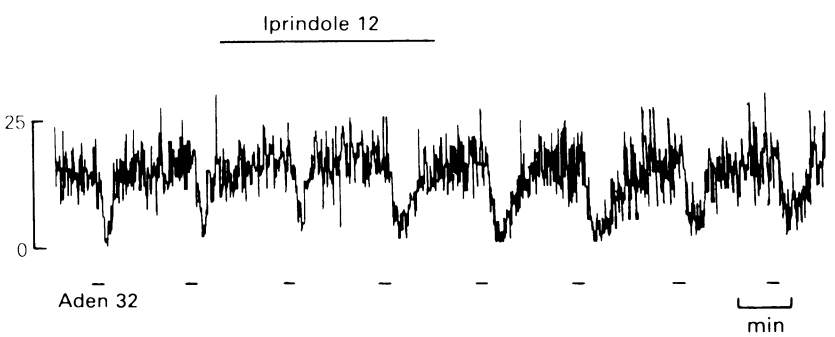

Figure 3 Potentiation of the depressant actions of adenosine (Aden, 32 nA) on the firing of a rat cerebral cortical neurone by iontophoretically applied iprindole (12 nA).

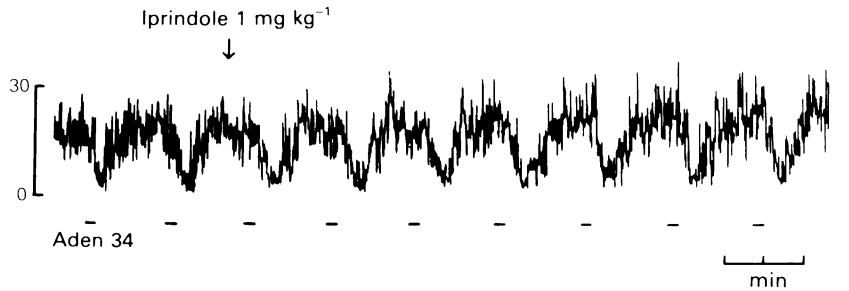

Figure 4 Potentiation of the depressant actions of adenosine (Aden, 34 nA) by intravenously administered iprindole (1 mg kg^{-1}).

increase in duration of 12.4 s ($P<0.001$). An example of the effects of iontophoretically applied iprindole is illustrated in Figure 3. The effects of iprindole on adenosine persisted for 20–30 min after its application.

Iprindole was administered intravenously to 4 rats in a dose of 1 mg kg^{-1}. In this amount, iprindole did not affect the spontaneous firing rate, but did enhance adenosine (Figure 4). The mean duration for the adenosine controls of the 4 neurones tested was 60.4 ± 4.2 s. After iprindole, the mean duration of the adenosine responses was increased to 96.7 ± 8.2 s ($P<0.05$).

As a control for the specificity of antidepressant-elicited enhancement of adenosine responses, 16 cells were tested for interaction between iprindole and 5'-N-ethylcarboxamide adenosine (NECA), an adenosine analogue which is not an effective substrate for the adenosine transport system in brain cell membranes. In these experiments, iprindole, applied for periods of up to 10 min, failed to enhance the duration or amplitude of NECA-evoked inhibitions (control depression = 101.2 ± 2.3 s; post-iprindole depressions = 97.6 ± 2.3 s; $P<0.1$). On several of these neurones there was evidence for some reduction of NECA-evoked responses during the period of iprindole application. This persisted during the immediate post-application period and may account for the small decrease in the duration of NECA-evoked inhibitions.

Chlorimipramine

The interactions between adenosine and chlorimipramine were tested on 26 neurones. Potentiation of the duration of the adenosine response was seen with 25 of these. The mean duration of the control responses to adenosine was $85{\cdot}5 \pm 1.5$ s. After iontophoretic applications of chlorimipramine, the mean duration of the purine-evoked responses was 106.3 ± 1.3 s, an increase in mean duration of 20.8 s ($P<0.001$).

Chlorimipramine was tested with NECA on 9 cells, but again failed to enhance the duration of the purine-evoked depressions (controls = 89.2 ± 2.9 s; post-chlorimipramine depressions = 84.8 ± 2.8 s, $P>0.01$). As was observed with iprindole, there was some decrease in the amplitude of NECA-evoked inhibitions during the application of chlorimipramine.

Desipramine

Desipramine was tested on 22 neurones and en-

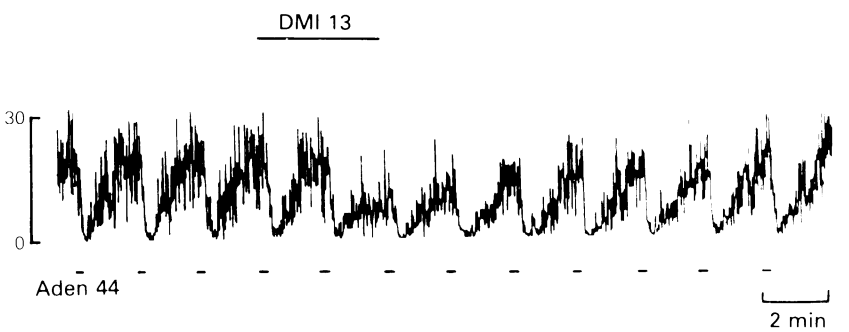

Figure 5 Potentiation of the depressant actions of adenosine (Aden, 44 nA) by iontophoretically applied desipramine (DMI, 13 nA).

hanced the depressant effects of adenosine on all of these. The control responses to adenosine had a mean duration of 68.5 ± 1.1 s. After desipramine the duration was increased to 88.5 ± 1.5 s, an increase in mean duration of 20 s ($P < 0.001$). An example of desipramine action is presented in Figure 5. Desipramine (13 nA for 4 min) enhanced the duration of adenosine-evoked depression of spontaneous firing. When recovery had occurred 22 min later, desipramine was applied again in the absence of adenosine applications. It did not alter the rate of spontaneous firing.

Antidepressants and caffeine

Caffeine competitively antagonizes the depressant action of adenosine in central neurones. It was therefore of interest to observe whether this methylxanthine would antagonize the depressant effect of the tricyclic antidepressants on the firing of cerebral cortical neurones. In experiments conducted on 9 animals, caffeine (24 and 48 mg kg^{-1}) was administered intraperitoneally after 2 control responses to chlorimipramine (5 animals) or desipramine (4 animals) had been recorded. In each instance, the depressant effects of chlorimipramine and desipramine were antagonized by caffeine. An example of this antagonism, recorded from one of these neurones, is presented in Figure 6. Chlorimipramine (31 nA) depressed the spontaneous firing of this neurone. Recovery to control firing rate was slow (> 25 min) after the first application but was accelerated when 24 mg kg^{-1} caffeine was administered during recovery from the second application of chlorimipramine. Subsequent responses to chlorimipramine were greatly reduced in magnitude (Figure 6b). Partial recoveries from the antagonism by caffeine began to be manifest some 3 h after caffeine administration.

Discussion

The cellular mechanisms of action by which the tricyclic antidepressants exert their clinical activity remain to be elucidated. An inhibition of the neuronal uptake processes for monoamines, especially noradrenaline, which would increase their concentrations in the synaptic regions has been proposed as an important factor (Garver & Davis, 1979). Delayed adaptive changes in the properties of adrenoceptors following chronic antidepressant treatment may account for the clinical observation that prolonged treatments of a week or more are required before therapeutic effects can be observed (Vetulani & Sulser, 1975). Electrophysiological studies have yielded conflicting data on the effects of tricyclic antidepressants on the responses of cerebral cortical neurones to noradrenaline. In some instances potentiation of the depressant effects of noradrenaline by desipramine have been observed (Bradshaw *et al.*,

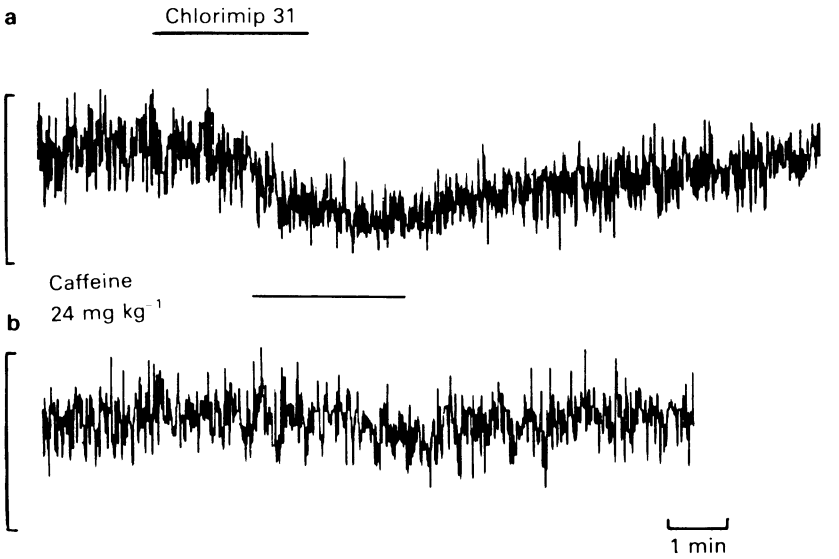

Figure 6 (a) Chlorimipramine (Chlorimip) application (31 nA) resulted in a reduction in the rate of firing of this cerebral cortical neurone. Recovery of firing to control levels had occurred 30 min after the application. (b) Ninety min after an intraperitoneal injection of caffeine (24 mg kg^{-1}) the depressant effects of chlorimipramine were substantially antagonized. Partial recovery to the effects of chlorimipramine had occurred 3 h after the administration of caffeine.

1974; Bunney & Aghajanian, 1976; Jones & Roberts, 1979; Hauser *et al.*, 1984). In contrast, Ewart & Logan (1978) and Stone & Taylor (1979) have reported that antidepressant drugs primarily reduce the response of cortical neurones to noradrenaline.

Since the realization that the mechanism of action of the clinically useful antidepressants could not be entirely explained by the inhibition of neuronal uptake of noradrenaline, other hypotheses have been proposed. For instance, a correlation has been proposed with the α-adrenoceptor blocking potency of the antidepressants (U'Prichard *et al.*, 1978), or their antagonism of central actions of histamine (Kanof & Greengard, 1978).

An additional mechanism of action involving adenosine was suggested by Sattin (1981, 1984). On the basis of observations that antidepressant drugs enhance brain levels of cyclic AMP by a theophylline-sensitive mechanism (Kodama *et al.*, 1971; Berndt & Schwabe, 1973; Huang & Daly, 1974; Sattin *et al.*, 1978; Kant *et al.*, 1983), Sattin has proposed that antidepressant treatment with the tricyclic agents may act, in part, by enhancing the effect of endogenous adenosine. Nortriptyline, iprindole and desipramine were particularly effective in enhancing cyclic AMP levels in the rat cerebral cortical tissue. Further support for this hypothesis came from electrophysiological experiments in which a number of iontophoretically applied tricyclic antidepressants were observed to enhance adenosine-elicited depressions of rat cerebral cortical neurones (Sattin *et al.*, 1978; Stone & Taylor, 1978). Sattin (1981) suggested that the tricyclic drugs increase cyclic AMP in brain tissue by bringing about the degradation of ATP with a consequent rise in both intra- and extracellular adenosine. Adenosine is a potent stimulant of adenylate cyclase. The mechanism by which the tricyclic agents could induce dephosphorylation of adenine nucleotides was not clarified.

Studies on the uptake of adenosine have demonstrated that the tricyclic antidepressants, like the structurally related phenothiazines with which they share many central actions, are inhibitors of adenosine uptake (Phillis & Wu, 1982a,b). From this observation it was possible to formulate a slightly different hypothesis, namely that the tricyclic compounds elevate extracellular adenosine levels by preventing its uptake into neuronal and glial elements (Phillis & Wu, 1982a, b). An elevation of extracellular adenosine levels could account for both the sedative actions and the elevation of cyclic AMP observed after acute administration of the tricyclic antidepressants.

The present work confirms and extends the original observations of Stone & Taylor (1978) in several important respects. As a result of a minor technical change in the solutions (inclusion of 50 mM NaCl) used for microiontophoretic ejection of the antidepressants, it has been possible to circumvent the problem of blocking electrode barrels described by Stone & Taylor (1978) and a very high proportion of cortical neurones responded to these agents with potentiated adenosine responses. A limitation of the iontophoretic technique is a lack of knowledge of the concentration of ejected drugs in the vicinity of the electrode tip. By administering agents systemically and observing a potentiation of iontophoretically applied adenosine, it is possible to draw some conclusions about drug concentrations in the brain. Intravenously administered nortriptyline and iprindole ($1\ mg\ kg^{-1}$) were observed to enhance the effects of locally applied adenosine. This is well within the dose range used to elicit behavioural effects in animals (Moller-Nielsen, 1980).

Evidence is steadily accumulating that the tricyclic antidepressants are concentrated in brain tissue at higher levels than in plasma in both man and laboratory animals. Brain levels of amitriptyline and nortriptyline in fatal cases of amitriptyline poisoning of humans are 9–18 times higher than those in the blood (Kristinsson *et al.*, 1983). Brain amitriptyline levels in these individuals reached 150 μM concentrations. Depressed patients treated with amitriptyline (150 mg daily) have plasma levels of both amitriptyline and nortriptyline of $20–262\ ng\ ml^{-1}$ (Rickels *et al.*, 1983). Similar blood levels of nortriptyline and amitriptyline were reported in another group of patients receiving amitriptyline (100–125 mg daily) (Borison *et al.*, 1982). Comparable levels of desipramine were observed in depressed patients being treated with this agent (Simpson *et al.*, 1983). It can be anticipated that brain concentrations in these patients would have been about 10 times higher (1–10 μM).

Animal studies reinforce human findings of a higher concentration of the tricyclic antidepressants in brain tissue than in plasma. Jori *et al.* (1971) observed brain concentrations of imipramine and desipramine that were 6–17 times greater than those in plasma. After a $5\ mg\ kg^{-1}$ intravenous dose, rat brain imipramine levels were 41 times higher than those in plasma (Bickel *et al.*, 1983), reaching peak concentrations of 100 μM. Desipramine concentrations in the brains of rats receiving $2.5–40\ mg\ kg^{-1}$ intraperitoneally ranged between 0.46 and $38\ \mu g\ g^{-1}$ of brain (1.7–140 μM) (Hrdina & Dubas, 1981; Biegon & Samuel, 1979).

The brain concentrations of intravenously administered nortriptyline and iprindole in the animals in the present study were, therefore, likely to have been sufficient to reduce significantly adenosine uptake by brain neuronal and glial cells. The IC_{20} values

for inhibition of adenosine uptake into rat cerebral cortical synaptosomes by nortriptyline and iprindole were 10^{-6} and 10^{-5} M respectively (Phillis & Wu, 1982a,b). Inhibition of adenosine uptake would readily account for their potentiation of the inhibitory effects of adenosine on neuronal firing. The lack of effect of chlorimipramine and iprindole on NECA-elicited depression of firing is consistent with this explanation, in that NECA is a poor substrate for the adenosine transport system (Wu *et al.*, 1984). Larger applications of the four antidepressants used in the study caused a depression of neuronal firing which was antagonized by the adenosine receptor blocker, caffeine, suggesting that this depression resulted from an enhancement of the extracellular levels of endogenously released adenosine.

Although the role of adenosine in the antidepressant effects of the tricyclic compounds remains to be established, the data presented in this paper suggests that adenosine may be critically involved in many of the central actions of acutely administered antidepressants. Adenosine and its analogues are known to reduce locomotor activity, promote sedation and to have analgesic actions (Phillis & Wu, 1981), properties that are shared with the antidepressants (Moller-Nielsen, 1980; Kawasaki *et al.*, 1979; Rigal *et al.*, 1983). Adenosine is therefore likely to play a role in the central actions of the antidepressants. Sattin (1984) has suggested that adenosine itself may be involved in the affective disorders and this proposal warrants further consideration. Neil *et al.* (1978) have demonstrated a failure of patients who are coffee users to respond to conventional antidepressant therapy and Sattin (1984) has reported anecdotal evidence to suggest a pharmacodynamic induction of behavioural disorders by caffeine. Adenosine may therefore be involved in the affective disorders.

In conclusion, the findings presented in this paper argue strongly for a purinergic link in some of the actions of the tricyclic antidepressants as a result of their inhibitory actions on adenosine uptake. The involvement of adenosine in antidepressant action is of clinical significance in that patients should be advised to avoid caffeine and theophylline-containing foods, beverages and medications.

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