increased depolarization of cholinergic terminals than in other brain regions (Sherman et al 1978; Murrin & Kuhar, unpublished results). This suggests that the effects of propranolol are particularly strong.

The localization of β-adrenoceptors in the striatum and how they modulate cholinergic function is not clear. It has been shown that they do not diminish after kainic acid lesions (Zahniser et al 1979), suggesting that the receptors are not on the cholinergic neurons themselves. Thus β-adrenoceptor stimulation may act indirectly on cholinergic neurons, perhaps by altering the release of another neurotransmitter. While a decrease in dopamine release, as suggested by the data of Morinan & Leonard (1977), would be consistent with an increase in cholinergic activity, there is recent evidence which indicates this may not be the mechanism of propranolol's action (Reisine et al 1982). At this time the dominant site for propranolol's effect on cholinergic neurons remains to be established.

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Antinociceptive effects in the rat of an adenosine analogue, N^6-phenylisopropyladenosine

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Purine derivatives such as adenosine occur in the central nervous system (c.n.s.) with a uniform distribution. In the c.n.s. adenosine inhibits neuronal firing, transmitter release and alters receptor sensitivity (see e.g. Stone 1981). It has been suggested that the purine derivatives as a group could form a more general synaptic control system in the c.n.s. and modulate neuronal activity. Thus, compounds in this group do not appear to act as neurotransmitters in the conventional sense (see Stone 1981).

Recently several potent adenosine analogues have been described which possess a high selectivity for membrane adenosine receptors (Fredholm 1980; Dunwiddie & Worth 1982). N^6-Phenylisopropyladenosine (PIA) is an analogue which has a relative selectivity for the A1 receptor, according to the subclassification in A1 and A2 receptors by Van Calker et al (1979) (Schwabe & Trost 1980). At the A1 site, xanthine derivatives like theophylline act as competitive inhibitors (Williams & Risley 1980; Dunwiddie & Worth 1982).

In order to investigate the potential antinociceptive effects of adenosine analogues we studied the effects of PIA on the tail flick response in rats. To further characterize the specificity of the analgesia induced via adenosine mechanisms, we also tested the reversibility by theophylline.

Methods

Adult Sprague-Dawley rats, ca 325 g, were used. Before the experiments the rats were kept in the laboratory given free access to rodent standard pellets and tap water. Each animal was used for one experiment only.

The analgesic response to PIA was determined using a tail-flick procedure (D'Amour & Smith 1941). Control response (mean of three consecutive tests) was adjusted between 2·00–3·00 s. To prevent tissue damage, cut off time in absence of a response was 7·0 s. PIA (L-form, Boehringer-Mannheim AG, Germany) was administered subcutaneously (s.c.) 0·3 mg kg^{-1}. Tail flick response was then tested each 2½ min during

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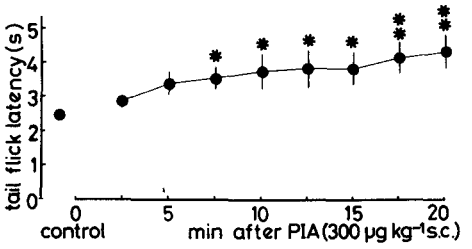

FIG. 1. Effects of PIA (L-form) on tail flick response in rats. PIA was given s.c. 0·3 mg kg^{-1}. Shown are means ± s.e.m., n = 7. $^{*}P < 0{\cdot}05$, $^{**}P < 0{\cdot}01$.

20 min. The rats were then injected s.c. with theophylline 50 mg kg^{-1} (Pharmacopoea Nordica) and tested for another 5 min.

Conventional methods were used for the calculation of means ± s.e.m. Statistical differences were calculated with one way analysis of variance followed by *t*-test or paired *t*-test. A *P*-value of 0·05 or less was considered significant.

Results

The effects of an s.c. injection of PIA on tail flick latency is shown in Fig. 1. The antinociceptive effect developed gradually during the trial and 20 min after PIA injection tail flick latency was approximately 80% increased compared with controls. 20 min after PIA when the antinociceptive effect was considered maximal or near maximal, theophylline, 50 mg kg^{-1} s.c., was given. Within 5 min, the PIA-induced analgesia was rapidly reversed and tail-flick latency returned to base line values (PIA + theophylline 2·45 ± 0·13 s vs base line control 2·45 ± 0·08 s, n.s.).

Discussion

Stable adenosine analogues like PIA induce several physiological and behavioural actions after parenteral administration. Thus, this compound causes sedation, decreased motor activity, hypothermia, bradycardia, hypotension and respiratory depression (Vapaatalo et al 1975; Snyder et al 1981; Dunwiddie & Worth 1982; Hedner et al 1982).

One area which as yet has received little attention relates to the possible involvement of adenosine in the perception of pain. However, an analgesic effect of PIA was suggested in the early study by Vapaatalo et al (1975) where they reported an increase in hot plate escape latency by approximately 100% after administration of 0·2 mg kg^{-1} L-PIA intraperitoneally to mice. Our findings are in agreement with these results. The antinociceptive effect was rapid in onset and was sustained for more than 20 min. The analgetic effect is most probably of central nervous origin as the tail flick response is considered to be spinally mediated. This is also suggested by recent data (Yarbrough & McGuffin-Clineschmidt 1981) showing that intracisternal administration of adenosine itself as well as adenosine analogues like 2-chloroadenosine caused dose-related increases in hot plate reaction times in mice.

Methylxanthines like theophylline act as competitive inhibitors on the binding of adenosine or adenosine analogues to the A1 receptor (Williams & Risley 1980; for terminology on adenosine receptors see Londos & Wolff 1977; Van Calker et al 1979; Stone 1981). Theophylline rapidly and completely antagonized the PIA-induced antinociceptive response suggesting that this may be an effect related to the A1 receptor.

In conclusion, the antinociceptive effects of adenosine analogues seem to be receptor-mediated events presumably elicited within the c.n.s. Needless to say, the potential analgesic effects of various adenosine analogues deserve further investigation.

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