Inhibition of Gastric Erosion Formations in Rats by Adenosine, 5 /-Adenosine Monophosphate and 5 /- Adenosine Diphosphate

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Abstract

Gastric erosions were induced in rats with indomethacin, 5-hydoxytryptamine (5-HT) or reserpine. Three adenine compounds adenosine, adenosine, 5 /-adenosine monophosphate (AMP) and 5 /- adenosine diphosphate (ADP) were found to protect against the erosion formations. Both 5-HT and reserpine caused untimely deaths of some of the control animals. Also the adenine compounds prevented the untimely deaths caused by the two ulcerogenes.

Keywords: Adenosine, AMP, ADP, Anti-ulcer, Antidote, Gastric erosion

Introduction

Besides their physiological functions in metabolism, adenosine and its related nucleotides are known to regulate the function and integrity of many tissues (Schubert, 1988). It is now known that adenosine and its related nucleotides lead to a burst in the synthesis of prostacyclin (Boeynaems *et al*., 1988), an anti-ulcer agent (Whittle et al., 1978). Furthermore it has been shown in this laboratory that an *Abrus* seed substance (Nwodo, 1985) whose mechanism of action is similar to that of adenosine and AMP, exerts anti-ulcer effects. Ulcer is a stress related disorder (Nwodo, 2000) and adenosine under stress conditions. It depresses signal transmission and inhibits gastric acid secretion (Gerber *et al.,* 1985). The possibility that these purines exert anti-ulcer effect was thus investigated.

Materials and Methods

Chemicals: Adenosine, 5/- adenosine mono-phosphate (AMP) and 5/-adenosine diphosphate (ADP), both disodium salts; indomethacin (all Sigma); 5-hydroxytryptamine (Koch-Light), reserpine (Ciba) and sodium bicarbonate were used.

Indomethacin induced ulcers: Four groups of 10 inbred Wistar albino rats (100 – 150) of either sex were deprived of food for 18h and treated per orally with normal saline (0.85% NaCl, 5 ml/kg), adenosine, (each 1mg/kg in 5ml/kg normal saline). Thirty minutes later each animal was given a subcutaneous injection of indomethacin (30 mg/kg in 1 ml normal saline containing 0.1ml 0.1M $NaHCO_3$). Seven hours afterwards the animals were sacrificed and scored for ulcers based on the incidence and severity of gastric erosions as described by Aguwa and Mittal (1981).

5-Hydrxytryptamine induced ulcers: Four groups of 10 rats per group were deprived of food for 18h and then treated as above with saline, adenosine, AMP and ADP. Thirty minutes later, each rat was served i.p with 5-HT (8 mg/kg in 1 ml normal saline). After 7h rest each animal was sacrificed and scored for ulcer as before.

Reserpine induced ulcers: In this model fasting was for 36h. Subcutaneous injections of indomethacin were replaced by i.p. administrations of reserpine (8 mg/kg in 1ml normal saline). All other procedures were as above.

Results

Effect on indomethacin induced ulcers: Single subcutaneous injections of indomethacin (30 mg/kg) induced gastric erosions in all test animals (Table 1). Severe erosions, indicated by high ulcer index, were observed in all saline treated rats (controls). Per oral treatments with adenosine, AMP and ADP (each 1 mg/kg) caused significant reductions in gastric damage scores. The level of significance in each case was $p < 0.001$.

Table 1: Inhibition of indomethacin induced ulcer by adenosine, AMP and ADP

Treatment	Dose	No. of Deaths	Ulcer Index
Normal Saline	5ml/kg	Nil	2.17±0.09*
Adenosine	1 mg/kg	Nil	0.78 ± 0.04*
AMP	1 mg/kg	Nil	1.11±0.06*
ADP	1 mg/kg	Nil	1.63± 0.10*

** = p < 0.001, i.e. significantly different from controls*

Inhibition of 5-HT induced effects: All the surviving rats that were treated with 5-HT (8 mg/kg) showed up with gastric erosions within 7h.Before the end of the 7h-treatment period, 30% of the control animals that received normal saline died (Table 2). Furthermore, single per oral treatments of rats with adenosine, AMP and ADP (1 mg/kg each) respectively, prevented the untimely deaths and greatly protected against 5-HT induced erosions of the stomachs (Table 2).

Suppression of reserpine induced gastric erosions: Single intra peritoneal doses of reserpine produced severe erosions of the stomachs as shown by high ulcer index (Table 3). Among saline treated rats 10% of them died before the end of the 7h-resting period. *Per oral* administrations of the purines adenosine, AMP and ADP (each 1 mg/kg) respectively prevented this early death and caused great reductions of the ulcer index (Table 3).

Table 2: Inhibition of 5-HT induced ulcers

Treatment	Dose	No. of Deaths	Ulcer Index
Normal Saline	5ml/kg	3 out of 10	1.74±0.06*
Adenosine	1 mg/kg	Nil	0.66±0.06*
AMP	1 mg/kg	Nil	0.98 ± 0.04*
ADP	1 mg/kg	Nil	1.24 ± 0.04*

** = p < 0.001, i.e. significantly different from controls*

Table 3: Inhibition of reserpine induced ulcers

Treatment	Dose	No. of Deaths	Ulcer Index
Normal Saline	5ml/kg	1out of 10	1.97±0.11
Adenosine	1 mg/kg	Nil	0.83 ± 0.18*
AMP	1 mg/kg	Nil	1.04 ± 0.07*
ADP	1 mg/kg	Nil	1.37 ± 0.04*

** = p < 0.001, i.e. significantly different from controls*

Discussion

Inhibition of drug induced gastric erosions by adenosine and its related nucleotides demonstrate the anti-ulcer capacity f these adenine compounds. Their order of activity viz: adenosine > AMP > ADP may reflect affinity for their receptors or transport mechanisms. Alternatively it indicates that adenosine is the final mediator of these compounds because ecto-nucleotidases of outer cell surfaces and endo-nucleotidases degrade the adenine nucleotides sequentially to adenosine. It is now well established that some inhibitory purinergic nerves whose transmitter substance is probably adenosine are widely distributed in the mammalian gastric gastro-intestinal tract (Burnstock, 1972). These findings and the abundance of adenosine receptors in the gastric mucosa (Burnstock and Brown, 1981) and parietal cells (Gerber *et al.,* 1985) indicate that a major endogenous function of this class of compounds and their analogues is protection against gastro-intestinal lesions. Gastric hyper secretion is an aggressive factor involved in the pathogenesis of some gastric and duodenal disorders (Wolfe and Soll, 1988 and it is now known that adenosine inhibits gastric acid secretion (Gerber *et al.,* 1985; Nwodo et al; 2008).

The exact electrophysiological mechanism by which they produce anti-ulcer effect is not known. But it is thought that inhibition of calcium availability underscores this function. Another factor that may improve upon perfusion of ischemic areas is their antagonism of microvasculature constrictor responses to endogenous neuro-humours especially as adenosine accumulation is a tissue response to hypoxia (Ribelayga and Mangel, 2005). In addition, they may promote prostaglandin mobilisation and so inhibit gastric acid secretion. Clinical studies suggest that changes in endogenous levels of adenosine could influence gastric secretion and ulcer formation (Yip and Kwok, 2004). Adenosine and its related nucleotides may serve additional function of protecting against toxicities due to some exogenous agents and fluctuations in neuro-humour levels as they manifested on the ulcerogenes. Thus they possess antidote properties.

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