INTERNATIONAL JOURNAL OF NATURAL AND APPLIED SCIENCES (IJNAS), VOL.2 NO. 2(2007); P. 46 – 49, 1 TABLE, 1 FIG.

Cytoprotective effect of adenosine monophosphate against indomethacin – induced ulcer in albino rats

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ABSTRACT

Gastric ulceration induced with 30mg/kg indomethacin was inhibited by 1mg/kg adenosine monosphosphate (AMP) in albino rats. The mean ulcer score was significantly reduced in both AMP treated rats (4.8 ± 0.41) and cemitidine treated rats (9.0 ± 0.71) $p<0.05$) "when compared with the control (31.60 ± 2.17). the degree of ulceration also followed the same pattern. The results indicate that adenosine monophosphate may play physiological role as a cytoprotective agent.

INTRODUCTION

Until recently, the physiology and pharmacological roles of the adenine nucleotides in the body were obscure and poorly understood (Brunton, 1996). Not much was indeed known about their endogenous biological functions (Rang et. al., 2000). The development of new and sensitive analytical techniques has opened up very interesting body of knowledge about these agents. Among these is the characterization of the purinergic receptors and neurotransmitters (Brown and Collis, 1983). These have helped to answer a number of questions which hitherto were speculative. The purinergic receptor have been indentified in different regions of the CNS, especially the cortex (Hoffman et. al., 1996) where they play a role as signaling molecules and in the dilatation of cerebral arterioles and modulation of cerebral functions (Bloom. 1996). They have also been found in the peripheral nervous system, especially in the viscera (Brown and Collis, 1982; Rang et. al., 2000). Their participation in the modulation of the pharmacologic activities of some autocoids in the gastric mucosa is better understood. Reine et, al., (1994) showed that they inhibit the spasmogenic activity of acetylcholine (ACh), histamine (HA) and serotonin (5H-T) in the gut. Sachs and Shin (1995) demonstrated their ability to mitigate the release of gastric acid.

The non-steroidal anti-inflammatory drug. Indomethacin is popular in the management of rheumatoid arthritis and associated pain. One of the limitations of its use is in the induction of gastric ulcer (Yeoman and Tulassy, 1998). Which is time and dose dependent. This has been demonstrated in animal studied and clinical settings. In both situations, cimetidine, has been found useful as a standard agents for controlling the situation (Feldman and Burton 1990, Walt, 1992).

The pathphysiology of acid-peptic disease is associated with imbalance between spasmogenic and aggressive agents (e.g gastrin, pepsin, acid, histamine) and the endogenous cytoprotective agents (e.g. bicarbonate, purines, gastric mucus, PGE). Recent therapies have been directed at elevating the levels of cytoprotective agents as a means of controlling gastric acidity and treatment of peptic ulcer (Brunton, 1996; Inomata et al. 2006)

Previous studies in this area have been confined to the adenosine and ATP analogs. In this study the monophosphate derivative was employed to determine its possible role as a cytoprotective agent.

MATERIALS AND METHOD

The materials used include: Healthy wistar albino rats weighing 180 – 200g randomly selected from both sexes. They were obtained from the College of Medicine, Imo State University Animal House. Adenosine -5-monophsophate (AMP), product of Sigma Chemical co London, England. Indomethacin and cimetidine (200mg Tab) from Medrel pharmaceutical (Pvt) Ltd, Mumbai, India and SmithKline Beecham Company, Brentford, England respectively.

Preparation of chemicals and drugs: standard solution of various chemical/drugs were prepared and diluted to the required specifications.

The rats were kept under standard laboratory conditions of 12 hours light / dark cycle. They had unrestricted feed and water. The method of Waisman et al. (1985) was used. This conformed with the methods of Tan et al. (2005). The animals were divided into groups: control, standard and test groups. Each group consisted of five (5) animals.

Group one represented the negative and was administered 0.5

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milligram per kilogram body weight (mg/kg) of normal saline (NS) intra-peritonally (i.p). After 2 hours the animals were given 30mg/kg indomethacin i.p. the drug was allowed to act for 24 hours and subsequently sacrificed by either overdose. By laparectomy the stomachs were examined and the degree of ulceration [summation of area of ulcers = lengths x width of each ulcer lesion (mm^2) Waisman et. al. (1985), Ashiwel (2006) Who estimated using a dissecting microscope (x 20. 1 x 1 eye-piece).

The ulcer lesions appeared like open wounds. Some of them had blood clots on the surfaces. From the degree of ulceration, the ulcer score and ulcer index were calculated (stated on the table).

The same procedure as in group one was adopted for group two which received 300mk/kg (i.p) of cimetidine (Taganet, classical antiulcer drug) in place of normal saline; and group three which was administered 1.0mg/kg of AMP instead of NS. Group two represented the positive control/standard, while group three represented the test group. The degrees of ulceration were also evaluated as in group one. The statistical evaluation was done using ANOVA and the student's t-test.

RESULTS

Table 1 showed that 1mg/kg of AMP given intraperitionally abolished the gastric mucosa erosion caused by the administration of 30mg/kg indomethacin in rats. The mean ulcer score for the negative control was 31.60 ± 2.17 when compared with the test group which gave a mean ulcer score of 4.8 ± 0.41; representing 84.8% reduction. This level of reduction is an improvement over the standard which attenuated the ulcer score by 71.5%.

Table 1. The effect of NS, Cimetidine and AMP on Indomethacin-induced Ulcer in Rats.

Treatment Group	Treatment animals	Mean No. of Ulcers	Degree of Ulceration (mm^2)	Ulcer Score	Ulcer Index ($x10^{-1}$)
Normal Saline	1	32	(3x3)+(7x2)+22x1)	45	4.5
	2	33	(8x3)+(9x2)+(16x1)	58	35.8
	3	10	(0x3)+(1x2)+(9x1)	11	1.1
	4	23	(0x3)+(1x2)+(14x1)	36	3.6
Mean±SD	5	06	(0x3)+(2x2)+(4x1)	8	0.8
		20.8±10.60		31.60±2.17	3.16±2.17
Cimitidine	1	10	(1x3)+(2x2)+(7x1)	14	1.4
	2	09	(4x3)+(2x2)+(3x1)	19	1.9
	3	05	(0x3)+(0x2)+(5x1)	05	0.5
	4	02	(0x3)+(1x2)+(1x1)	03	0.3
	5	02	(1x3)+(0x2)+(1x1)	04	0.4
Mean±SD		6.5±3.6		9.00±0.71	0.90±0.71
AMP	1	06	(0x3)+(2x2)+(4x1)	08	0.8
	2	04	(0x3)+(2x2)+(2x1)	06	0.6
	3	07	(0x3)+(2x2)+(5x1)	09	0.9
	4	01	(0x3)+(0x2)+(1x1)	01	0.1
	5	00	(0x3)+(0x2)+(0x1)	00	0.0
Mean±SD		3.6±3.00		4.8±0.41	0.48±0.41

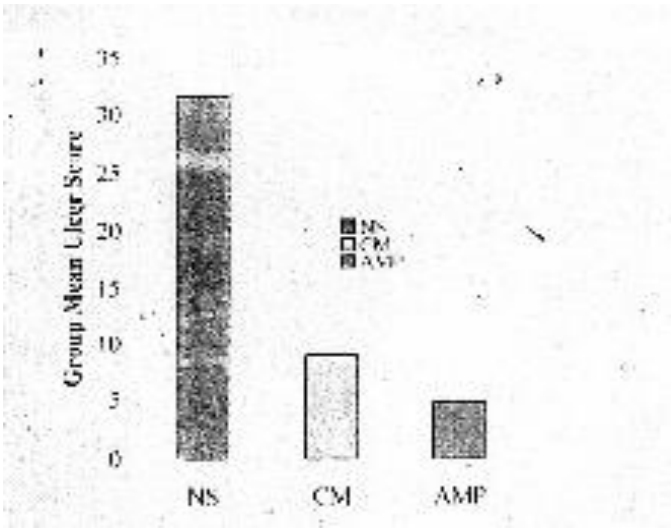

Fig.1. Effect of NS,cimetidine and AMP on indomethacin – induced ulcer in rats

DISCUSSIONS

The neurons associated with the enteric plexus are known to secret ACh, noradrenaline (NA), PGs, 5HT, purines, nitric oxide (NO) and other pharmacologically active peptides (Ranf et, al,. 2000). The action of the spasmolytic secretions regulates those of the spasmogenic secretions. The unmodulated release of the spasmogens has been implicated in the etiology of gastric erosion, ulceration and sometimes bleeding (Brunton, 1996). On the other hand, the paracrine stimulation (sometimes by ACh) leads to the release of spasmogenic local hormones such as HA from the enterochromaffin cells. This contributes to gastric ulceration (Rang et, al,. 2000). The endocrine activities of gastrin from the antral G-cells also cause the release of HA. Cimetidine and related drugs have successfully been used as antiulcer drugs (Binder and Donaldson, 1978; Walt, 1992). They are HA – H_2 receptor Blockers.

The parietal cells of the gut are the only cells in the body that contain H^+, K^+ - ATPase activity (Brunton, 1996). The stimulation of this enzyme CAMP or Ca^{2+} leads to the accumulation of H^+ in the gastric lumen, thereby raising its acidity. The consequence is the erosion of the gastric mucous membrance. This explains why antacids are useful in the management of gastric ulcers because they are capable of neutralizing the gastric acid, however, Omeprazole is more effective in this regard because it covalently inhibits H^+, K^+ - ATPase activity (Yoeman, and Tulassy, 1998).

The recent approach to ulcer therapy involves the inhibition of CAMP and the stimulated release of gastric mucus and bicarbonate, which have been found to be cytoprotective against gastric ulceration (Sachs and Shin, 1995). Bismuth chelate, sucralfate and mesoprostol (PGE) are clinically used as antinuclear drugs because of the above property (Rang et, al,. 2000). Indomethacin blocks the synthesis of the PGs to cause gastric ulceration. Studies show that adenosine and ATP possess gastro intestinal cytoprotective action (Williams et, al., 1994). We did not come across any such studies for AMP.

In this study gastric ulceration and bleeding were observed in the N.S treated group. But 1mg/kg intraperitionally administered AMP significantly protected the rats against gastric ulceration ($P<0.05$). This result agrees with the work of Lindberg et, al,. (1990) using adenosine in guinea pigs. The degree of ulceration and the ulcer score were significantly attenuated in the test group by 83% and by 67% in the animals treated with cimetidine when compared with the control (see table and bar chart). The attenuation of the degree of ulceration was also found to be greater in the test than the standard cimetidine by 45%. The mean ulcer score was 9.00 = 0.41 in the test, representing a 42% difference in favour of the test agent. The ability of AMP to protect against the development of ulceration may be associated with the property of the purines to induce the secretion of gastric mucus and bicarbonate (Rang et, al., 2000). It was reportd by Lindbery et, al. (1990) that the purines block the activity of H^+, K^+ - ATPase and the secretion of gastric thereby reducing the level of gastric H^+ ions and spasmogenic histaminic activity on the guts. The observed cytoprotective action of AMP may have followed a similar mechanism. However, the exact mechanism is unknown. Further work is underway to ascertain this.

In conclusion, the purine analog, Amp may indeed posses a cytoprotective action on the mucosal membrane of the guts. This action prevented the erosion and the possible ulceration of the rat stomach walls. The exact mechanism by which this happens is still speculative. Additional work is underway to ascertain this.

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