PROSTAGLANDINS AND 5-HT RESPONSE ON GASTRIC SECRETION IN ALBINO RATS

P.K. Debnath¹, Anjan Adhikari²*, Tapas Sur³, S.K. Bandyopadhyay⁴, T. K. Mandal⁵

ABSTRACT: Prostaglandins (PGE) 0.1, 0.2 and 0.4 mg/kg and 5-hydroxytryptamine (5-HT) 1, 2.5 and 5 mg/kg dose dependently inhibited gastric secretion in pyloric legated rats model. While PGF α 0.1, 0.4 and 1 mg/kg inhibited gastric acid secretion. Methysergide in the dose 0.05 mg/kg significantly stimulated the gastric secretion. When non-inhibitory dose of PGE₁ (0.1) and 5-HT (1.0 mg/kg) are injected simultaneously there were potentiation of inhibitory activity on gastric secretory response on volume, acid output, chloride output and pepsin output. The inhibitory activity of both PGE₁ (0.4 mg/kg) and 5-HT (5.0 mg/kg) including the inhibitory potentiating activity could not be modified by the pretreatment of methysergide (0.05 mg/kg). Similarly stimulatory dose of PGF₂α (0.4) mg/kg and inhibitory dose of PGE₁ (0.4 mg/kg) administered together inhibitory response of PGE₁ (0.4 mg/kg) were also not modified by methysergide pretreatment.

Key words: Prostaglandins, 5-HT, Gastric Secretion, Methysergide.

INTRODUCTION

Prostaglandins (PGs) and 5-Hydroxytryptamine (5-HT) both are found throughout the central nervous system (CNS) and gastro-intestinal tract (GIT) with synthesizing and metabolizing distinct PG and 5-HT type. Although, they show similar activity but their role in GIT and CNS are not well understood. PGE type and PGF type showed opposing effect in various experimental models both in CNS and GIT. Therefore, rather antagonistic effect of PGE₁ and PGF₂α were obvious. PGE₁ and 5-HT both inhibit gastric secretion while PGF₂α stimulate gastric secretion and in higher doses inhibit gastric secretion (Guha et al., 1979, Goel and Sanyal, 1983). In CNS level PGE₁ potentiate morphine analgesia and per se antinociceptive action of PGE₁ was found to be inhibited by PGF₂α (Bhattacharya et al., 1978; Sanyal et al., 1977).

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PGF$_2\alpha$ is known to inhibit the effects of several centrally acting drugs, namely hexobarbitone hypnosis, anticonvulsant effect of phenobarbitone and antonociceptive effect of cannabis where as these are potentiated by PGE$_1$. Further, PGF$_2\alpha$ activity was also inhibited by PGE$_1$ induced potentiation on the effects of these centrally acting agents. In the present study inter-relationship on the effect of Prostaglandins (PGE$_1$ and PGF$_2\alpha$) and 5-hydroxytryptamine (5-HT) on gastric secretion in pyloric ligated rats were determined.

**MATERIALS AND METHODS**

The effect of drugs was studied on gastric secretion in 4 h pyloric ligated rats. The stomach was removed after 4 h pyloric ligation and the gastric juice was collected and filtered through glass wool and centrifuged at 3000 rpm for 5 min. Supernatant was collected from centrifuged juice and its volume was expressed as ml/100 g body weight. Total acid was determined by titrating the gastric juice with N/100 NaOH using phenolphthalein as indicator and concentration was expressed as µEq/ml and output as uEq/4h (Hawk 1965, Sanyal et al., 1971). The peptic activity was determined using hemoglobin as substrate as per the method described earlier (Debnath et al., 1974) and concentration was expressed as µmol tyrosine/ml and output as µmol of tyrosine/4h.

**Drugs and Pre-treatment:** PGE$_1$, PGF$_2\alpha$ (Upjohn Company, USA) and 5-HT (Sigma) used 30 min and methysergide (Sandoz Basal) 60 min before pyloric ligation.

**RESULTS AND DISCUSSION**

Prostaglandin PGE$_1$ 0.1, 0.2 and 0.4 mg/kg and 5-HT 1, 2.5 and 5 mg/kg dose inhibited gastric secretion dose-dependently. The dose of PGE$_1$ (0.1 mg/kg) and 5-HT (1 mg/kg) showed no appreciable inhibition. While PGF$_2\alpha$ 0.1 and 0.4 mg/kg stimulated the gastric acid secretion on the contrary 1.0 mg/kg inhibited the gastric secretion. Methysergide in the dose 0.05 mg/kg stimulated the gastric acid secretion significantly. When non-inhibitory dose of PGE$_1$ and 5-HT are injected simultaneously there was potentiation of inhibitory activity of gastric secretary response on volume, acid output, chloride output and pepsin output. However, the inhibitory activity of both PGE$_1$ (0.4 mg/kg) and 5-HT (5 mg/kg) could not be modified by the pretreatment with methysergide (0.05 mg/kg). Similarly, when stimulatory dose of PGF$_2\alpha$ (0.4 mg/kg) and inhibitory dose of PGE$_1$ (0.4 mg/kg) were administered together, the inhibitory response of PGE$_1$ (0.4 mg/kg) could not be modified. Further, the gastric inhibitory potentiating activity of non-inhibitory dose PGE$_1$ (0.1 mg/kg) and 5-HT (1 mg/kg) could not also be modified by methysergide (0.05 mg/kg) in its stimulatory dose (Table 1).

In the present study gastric secretary response of 5-HT, PGE$_1$ and PGF$_2\alpha$ were screened. While PGF$_2\alpha$ showed stimulation of gastric acid secretion in small doses and inhibition in higher doses. Significant stimulatory and inhibitory dose of PGF$_2\alpha$ and PGE$_1$ respectively when administered together showed inhibitory activity. The inhibitory effect of PGE$_1$, 5-HT and PGF$_2\alpha$ or in combination could not be modified by methysergide. PGE$_1$ induced inhibition of gastric secretion has been shown to be 5-HT mediated response. PGF$_2\alpha$ on the other hand stimulate basal and pentagastrin stimulated gastric acid secretion in anaesthetized and in conscious rats (Guha et al., 1979; Goel and Sanyal 1983).
Table 1: Effect of Prostaglandins and 5-Hydroxytryptamin response on gastric secretion in Albino rats.

<table>
<thead>
<tr>
<th>Group* Dose mg/kg</th>
<th>No</th>
<th>Volume ml/100g</th>
<th>Free acid mEq/l</th>
<th>Total acid mEq/l</th>
<th>Total acid output iEq /4h</th>
<th>Chloride Concentration mEq/l</th>
<th>Chloride output mEq/4h</th>
<th>Pepsin Concentration imol/tyrosine</th>
<th>Pepsin Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>28</td>
<td>2.97 ±0.25</td>
<td>58.4 ± 6.2</td>
<td>89.6 ±4.3</td>
<td>291.7±31.5</td>
<td>134.5±4.7</td>
<td>389.1±41.5</td>
<td>409 ±34</td>
<td>1023 ±97</td>
</tr>
<tr>
<td>PGE₁ 0.1</td>
<td>10</td>
<td>2.90±0.20</td>
<td>63.7 ± 9.9</td>
<td>98.2 ±6.9</td>
<td>262.4±54.4</td>
<td>139.9±4.8</td>
<td>374.0±25.2</td>
<td>420 ±26</td>
<td>1206 ±91</td>
</tr>
<tr>
<td>PGE₁ 0.2</td>
<td>8</td>
<td>2.18 ±0.19</td>
<td>46.1 ±7.3</td>
<td>93.9 ±7.5</td>
<td>203.1±27.8</td>
<td>146.4±3.5</td>
<td>326.2±34.7</td>
<td>511 ±29</td>
<td>1083 ±9</td>
</tr>
<tr>
<td>PGE₁ 0.4</td>
<td>20</td>
<td>1.37 ±0.24a</td>
<td>21.6±4.6</td>
<td>47.4 ±4.4</td>
<td>66.7±9.1</td>
<td>124.5±3.6</td>
<td>174.2±16.6</td>
<td>588 ±29</td>
<td>758 ±61a</td>
</tr>
<tr>
<td>PGF₂α 0.1</td>
<td>10</td>
<td>3.10 ±0.24</td>
<td>61.2 ±6.3</td>
<td>83.7 ±7.2</td>
<td>358.3±21.7</td>
<td>142.2±6.4</td>
<td>402.7±31.2</td>
<td>483 ±39</td>
<td>1289 ±97</td>
</tr>
<tr>
<td>PGF₂α 0.4</td>
<td>8</td>
<td>4.61 ±0.31a</td>
<td>69.3 ±7.8</td>
<td>96.2 ±7.4</td>
<td>411.1±30.3</td>
<td>159.3±5.2</td>
<td>624.1±37.7</td>
<td>431 ±26</td>
<td>1675±104a</td>
</tr>
<tr>
<td>PGF₂α 1.0</td>
<td>8</td>
<td>1.90 ±0.25a</td>
<td>58.7 ±5.2</td>
<td>83.2 ±6.1</td>
<td>202.2±19.4</td>
<td>127.7±4.9</td>
<td>267.2±29.3</td>
<td>540 ±31a</td>
<td>1081 ±63</td>
</tr>
<tr>
<td>5-HT 0.1</td>
<td>8</td>
<td>2.37 ±0.25</td>
<td>57.7 ±7.5</td>
<td>86.3 ±6.8</td>
<td>201.6±28.1</td>
<td>124.8±4.3</td>
<td>289.3±21.9</td>
<td>504 ±46</td>
<td>1114 ±87</td>
</tr>
<tr>
<td>5-HT 0.5</td>
<td>9</td>
<td>1.59 ±0.20a</td>
<td>34.8 ±6.6</td>
<td>63.6 ±6.1</td>
<td>103.9±17.9</td>
<td>114.5±4.6</td>
<td>181.5±60.9</td>
<td>538 ±40</td>
<td>780 ±79a</td>
</tr>
<tr>
<td>Methy 0.05</td>
<td>10</td>
<td>4.10 ±0.24a</td>
<td>63.7 ± 6.3</td>
<td>101.8±4.0</td>
<td>420.5±37.2</td>
<td>161.5±3.4</td>
<td>665.1±49.5</td>
<td>447 ±38</td>
<td>1795±150a</td>
</tr>
<tr>
<td>5-HT + PG 1 + 0.1</td>
<td>12</td>
<td>1.52 ±0.29a</td>
<td>54.0 ± 6.7</td>
<td>79.6 ±5.8</td>
<td>126.4±22.1</td>
<td>110.0±2.7</td>
<td>167.9±21.4</td>
<td>532 ±40</td>
<td>692±134a</td>
</tr>
<tr>
<td>PGF₂α + 5-HT 0.4 + 5</td>
<td>10</td>
<td>1.61 ±0.26a</td>
<td>56.0 ± 6.5</td>
<td>79.6 ±5.8</td>
<td>101.4±23.1</td>
<td>108.0±2.5</td>
<td>157.9±20.2</td>
<td>512 ±41</td>
<td>632±124</td>
</tr>
<tr>
<td>PGE₁ + PGF₂α 0.4 + 0.4</td>
<td>10</td>
<td>1.66 ±0.25a</td>
<td>51.2 ± 4.9</td>
<td>86.4±6.3</td>
<td>86.3±18.3</td>
<td>114.4±4.5</td>
<td>156.8±34.6</td>
<td>542 ±38</td>
<td>748 ±86</td>
</tr>
<tr>
<td>Methy + 5-HT 0.05 + 5</td>
<td>8</td>
<td>1.13 ±0.22b</td>
<td>26.4±3.8</td>
<td>54.2±2.1</td>
<td>71.3 ±15.2</td>
<td>114.3±7.2</td>
<td>148.2±31.3</td>
<td>481±38</td>
<td>627 ±59b</td>
</tr>
<tr>
<td>Methy + PG E 0.05 + 0.4</td>
<td>15</td>
<td>2.30 ±0.21</td>
<td>53.4 ± 4.1</td>
<td>76.4±4.5</td>
<td>177.7±20.6a</td>
<td>139.6±2.7</td>
<td>314.3±36.1</td>
<td>560 ±63a</td>
<td>1573±161</td>
</tr>
<tr>
<td>Methy + 5-HT + PGE₁ 0.05 + 0.1</td>
<td>8</td>
<td>1.51 ±0.43a</td>
<td>44.2 ±7.1</td>
<td>63.3 ±6.8</td>
<td>106.8±46.6</td>
<td>103.4±1.7</td>
<td>159.2±44.4</td>
<td>532 ±42a</td>
<td>692±134</td>
</tr>
</tbody>
</table>

* Single dose treatment ; Values are mean ± S.E. P value a <0.05, b <0.01 in comparison to control Prostaglandin E₁ (PGE₁), Prostaglandin F₂α (PGF₂α), 5-hydroxytryptamine (5-HT), Methysergide (Methy).
The effect of PGE$_1$ on steady state level of 5-HT increased in brain but not in stomach and intestine. On the contrary, turn over of rat brain and stomach correlated well with the pharmacological activity to gastric secretion and CNS parameters. PGE$_1$ enhanced the rate of accumulation of serotonin in pargyline treated rats (Debnath et al., 1978) confirming an earlier report (Haubrich et al., 1973) in brain. PGF$_2$$\alpha$ *per se* in the dose 0.5, 1.00 and 2.0 mg/kg decreased the steady state level of brain 5-HT but the differences are significant only at the dose 1.0 and 2.0 mg/kg. The brain turn over was studied on accumulation of 5-HT at 30 min and 45 min with tranylcypromine were significantly increased while at 60 and 90 min came to normal level. In stomach tissue turn over is increased at 15, 30, 45 and 60 min, but came to normal by 90 min (Goel et al., 1985). The morphine analgesics (7.5 mg/kg) was antagonized by PGF$_2$$\alpha$ in the dose 2.00 mg/kg at 15 min while at 75 min potentates the analgesic activity (Katiyar and Debnath, 2013) corroborate with its effect on brain 5-HT turn over. In another study (Bhattacharya 1982) showed that centrally administered PGF$_2$$\alpha$ at the dose decreased the brain serotonin.

The higher dose of PGF$_2$$\alpha$ (1.0 mg/kg) did not show stimulatory activity on gastric secretion rather showed inhibition of gastric acid secretion of 5-HT type response. There is report of auto-conversion of prostaglandin one type to another (Ricciotti 2011). When PGE$_1$ inhibitory dose and stimulatory dose of PGF$_2$$\alpha$ were administered together, in spite of antagonism rather showed potentiating of inhibitory response. In smaller dose stomach 5-HT was decreased while in higher dose increased (Sanyal and Debnath, 1974; Debnath 1977). The inhibitory response of 5-HT and PGE$_1$ could not be blocked.

The alteration of 5-HT metabolism could produce clinical symptoms. Similarly, after small bowel resection, hyperacid secretion appear in man due to reduction in 5-HT secreting area (Aber et al., 1967).

Further, on continuous administration of pentagastrin the peak gastric secretory response is always followed by decrease in the secretory activity. It has already been shown in cats, rats and in man, this phenomenon of pentagastrin could be modified by drugs like methysergide, cypheptadine, reserpine and pCPA suggesting the involvement of 5-HT after pentagastrin (Sanyal and Waton 1972, 1976, Debnath et al., 1975, Goel et al., 1983). Rats pretreated with indomethacin, a potent drug known to significantly inhibit the biosynthesis of PGE$_1$, modified the phenomena of pentagastrin. Inhibitory response of PGE$_1$ was also blocked by pretreatment with reserpine and pCPA suggesting that the absence of optimal concentration of tissue 5-HT the inhibitory activity of PGE$_1$ was annulled (Goel et al., 1983; Debnath et al., 1975). Thus, the findings from the present investigation indicate that prostaglandin’s and 5-hydroxytryptamine work in conjunction to control the gastric secretory process. Both these mediators, when augmented reduce gastric secretion.

In certain clinical situations, increase or decrease concentration of PG and 5-HT could be correlated with gastric hypo and hyper secretion (Prasad et al., 1977, Gupta et al., 1977, 1980). Cypheptadine, apart from being a 5-HT antagonist, also possesses prostaglandin antagonist properties (Acharya et al., 1977). The exact nature of interaction between PGs and 5-HT and the receptor sub types involved in such interactions need to be delineated Keeping in
cognizance of earlier studies and in conjunction with the present investigation with clinical conditions on gastric secretion and on tissue and blood 5-HT levels extend support to fulfill the aims with objectivity for bridging the gaps on the role of PGs and 5-HT on the inhibition of gastric secretion.

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Prostaglandins and 5-HT response on gastric secretion in Albino rats.


