EFFECT OF PANAX GINSENG AND DIAZEPAM ON BRAIN 5-HYDROXYTRYPTAMINE AND ITS MODIFICATION BY DICLOFENAC IN RAT

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Abstract: Wistar male rats pretreated with anti-stress agents like, Panax ginseng (Pg) and diazepam (Diaz) were stressed by restraining for 1 h and 5-HT content of brain and hypothalamus as well as plasma corticosterone were measured spectrophotofluorometrically. Diclofenac (DICLO), a prostaglandin (PG) synthesis inhibitor was used to confirm the role of prostaglandin in restraint stress-induced elevation of central 5-HT correspondingly confirmed by elevation of plasma corticosterone and modification of the above anti-stress agents. Pg, Diaz and DICLO per se did not modify brain and hypothalamic 5-HT in control rats. But they attenuated stress-induced elevation of brain and hypothalamic 5-HT. Anti-stress action of both Pg and Diaz reflected by inhibition of stress-induced elevation of brain and hypothalamic content of 5-HT as also stress-induced concurrent elevation of plasma corticosterone were further diminished by DICLO. The mediatory action of 5-HT in anti-stress effects of Pg and Diaz may be modulated through prostaglandins.

Key words: restraint stress dicrofenac Panax ginseng corticosterone prostaglandin

INTRODUCTION

The prime reaction in stress is the activation of the hypothalamo-hypophyseal-adrenocortical axis (H-H-A axis). 5-HT plays an important role in the regulation of stress-induced activation of H-H-A axis (1–3). Stress also enhances the activity of central prostaglandins (4–5). The role of PGs in stimulation of the H-H-A axis has also been proposed (5–7). It has been reported that PGs enhance 5-HT level as well as 5-HT turnover (8–9).

Stress attenuating actions of diazepam and Panax ginseng are well documented (10–12). Earlier studies indicated that Panax ginseng (Pg) and diazepam (Diaz) in a dose dependent manner attenuated restraint stress-induced elevation of brain and hypothalamic 5-HT and simultaneously diminished restraint stress-induced

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enhancement of plasma corticosterone (13-15). But their definite effect on the modification of 5-HT during stress could not be confirmed.

The purpose of this study was to examine the central action of DICLO, PG synthesis inhibitor (16) on the modifying effects of Panax ginseng and diazepam on 5-HTergic neurotransmission during restraint stress, measured by brain and hypothalamic 5-HT estimation with simultaneous estimation of plasma corticosterone as an index of H-H-A axis stimulation.

METHODS

Wistar strain male albino rats (120-150 g) were used. They were either segregated into groups of 10 for estimation of 5-HT or into groups of 12 for hypothalamic 5-HT, while plasma corticosterone was done in all animals. As the hypothalamii of 3 rats were pooled together to obtain the 5-HT level in hypothalamus, 12 rats were taken instead of 10 animals in groups for estimation of 5-HT in hypothalamus.

The animals were subjected to restraint stress for 1 h (RSI) as described earlier by completely immobilizing them (13-15). The anti-stress agents, Diaz (0.2 mg/kg) and Pg (50 mg/kg) were given intraperitoneally 30 min before the animals were subjected to stress. Animals were pretreated with DICLO (15 mg/kg) intraperitoneally 6 h prior to the experiment. The doses and duration of each drug were chosen based on earlier studies (14-15).

Estimation of 5-HT on whole brain and hypothalami (pooled from 3 rats) was done spectrophotofluorometrically following the method of Amar et al (17). The measurement of 5-HT was done by reading the fluorescence at 495 nm, with activation at 385 nm (SPEKOL 11, Carl Zeis, GDR). Plasma 11-hydroxycorticosteroid was estimated fluorimetrically by the method of Mattingly (18). The readings were taken at 530 nm with activation at 470 nm.

All values were presented as mean ± SEM. Statistical comparisons were made by using Student "t" test. Statistical significance was considered as P<0.05.

RESULTS

Table I shows that in response to restraint stress (1h) there were elevations of 5-HT in brain (2.75 ± 0.12) and hypothalamus (3.28 ± 0.12) along with plasma corticosterone (71.28 ± 2.45), where as pretreatments with Pg, Diaz and DICLO and DICLO per se did not change these parameters in comparison to their respective control group.

Pg significantly reduced elevations of 5-HT in brain (1.98 ± 0.05), hypothalamus (2.24 ± 0.18) as also plasma corticosterone (58.18 ± 3.94) by RSI are shown in Table II. Similarly, Diaz reduced RSI-induced increases of 5-HT in brain (2.02 ± 0.06), hypothalamus (2.52 ± 0.22) as also plasma corticosterone (61.85 ± 1.52) which are shown in Table II. DICLO significantly diminished RSI-induced enhancement of 5-HT in brain (1.87 ± 0.08), hypothalamus (2.42 ± 0.24) as also plasma corticosterone (49.32 ± 3.85), shown again in Table II.
TABLE I: Effect of restraint stress, *Panax ginseng*, diazepam and diclofenac on brain and hypothalamic 5-HT and plasma corticosterone.

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Whole brain 5-HT* (n=10)</th>
<th>Hypothalamic 5-HT* (n=12)</th>
<th>Plasma corticosteroneb (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Control</td>
<td>0.85±0.03</td>
<td>1.74±0.16</td>
<td>32.12±2.12</td>
</tr>
<tr>
<td>2.</td>
<td>RSI</td>
<td>2.75±0.12**</td>
<td>3.28±0.12**</td>
<td>71.28±2.45**</td>
</tr>
<tr>
<td>3.</td>
<td>Pg</td>
<td>0.84±0.06</td>
<td>1.82±0.11</td>
<td>30.15±3.42</td>
</tr>
<tr>
<td>4.</td>
<td>Diaz</td>
<td>0.83±0.12</td>
<td>1.94±0.18</td>
<td>29.24±2.85</td>
</tr>
<tr>
<td>5.</td>
<td>DICLO</td>
<td>0.72±0.15</td>
<td>1.53±0.10</td>
<td>24.78±3.92</td>
</tr>
</tbody>
</table>

Values are expressed as Mean ± SEM

* = μg/g of wet tissue

** = μg/100 ml of blood

**P<0.001 as compared with control

TABLE II: Effect of *Panax ginseng*, diazepam on restraint stress-induced enhancement of brain and hypothalamic 5-HT and plasma corticosterone modification by diclofenac.

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Whole brain 5-HT* (n=10)</th>
<th>Hypothalamic 5-HT* (n=12)</th>
<th>Plasma corticosteroneb (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>RSI</td>
<td>2.75 ± 0.12</td>
<td>3.28 ± 0.12</td>
<td>71.28 ± 2.45</td>
</tr>
<tr>
<td>2.</td>
<td>RSI+Pg</td>
<td>1.98 ± 0.05**</td>
<td>2.24 ± 0.18**</td>
<td>58.18 ± 3.94**</td>
</tr>
<tr>
<td>3.</td>
<td>RSI+Diaz</td>
<td>2.02 ± 0.06**</td>
<td>2.52 ± 0.22*</td>
<td>61.85 ± 1.52*</td>
</tr>
<tr>
<td>4.</td>
<td>RSI+DICLO</td>
<td>1.87 ± 0.08**</td>
<td>2.42 ± 0.24*</td>
<td>49.32 ± 3.85**</td>
</tr>
<tr>
<td>5.</td>
<td>RSI+Pg+DICLO</td>
<td>1.54 ± 0.14*</td>
<td>1.57 ± 0.08*</td>
<td>39.68 ± 3.76**</td>
</tr>
<tr>
<td>6.</td>
<td>RSI+Diaz+DICLO</td>
<td>1.54±0.07**</td>
<td>1.74 ± 0.04*</td>
<td>45.25 ± 2.78**</td>
</tr>
</tbody>
</table>

Values are expressed as Mean ± SEM

* = μg/g of wet tissue

** = μg/100 ml of blood

**P<0.01; **P<0.001

Group 2, 3 & 4 are compared with Group 1; Group 5 is compared with Group 2; Group 6 is compared with Group 3

Table II also shows the effects of DICLO on the negating effect of Pg and Diaz on RSI-induced elevation of the same parameters. Significant accentuating effects of DICLO were thereby Pg antagonism of RSI-induced increases of 5-HT in brain (1.54 ± 0.07) and hypothalamus (1.74 ± 0.04) 5-HT as also elevation of plasma corticosterone (45.25 ± 2.78).

DISCUSSION

5-HT has been implicated in a variety of central neuronal system-mediated processes including anxiety and stress.
Under the influence of any stressor, producing non-specific responses, changes are brought about in the concentration, synthesis, metabolism and turnover rate of 5-HT in the brain (19-20). It has been known that PGs markedly enhance rat brain 5-HT levels as well as 5-HT turnover (5, 8-9).

Restraint stress enhanced brain and hypothalamic content of 5-HT and plasma corticosterone in rat upto 1 h. Prologation of stress (more than 1 h) could not induce further enhancement in this parameter, probably due to adaptive changes (13-15). All subsequent experimentations were done with animals restrained for 1 h only, as before.

In our earlier studies, it was noted that Pg and Diaz significantly reduced RSI-induced elevation of brain and hypothalamic content of 5-HT and plasma corticosterone (index of H-H-A axis activation) dose dependently, which justifies their anti-stress action (14-15).

Pg, Diaz and DICLO per se did not modify the control levels of brain and hypothalamic 5-HT and plasma corticosterone, showing negligible action on basal H-H-A axis function. DICLO, the PG synthesis inhibitor significantly diminished RSI-induced enhancement of brain and hypothalamic 5-HT as also plasma corticosterone. These observations point to the involvement of PGs in stress-induced enhancement of 5-HTergic neurotransmission supporting the hypothesis that PGs modulate 5-HTergic neurotransmission (6, 8, 13, 15) even during restraint stress. In this study significant accentuation of the inhibitory effects of Pg and Diaz on RSI-induced elevation of brain and hypothalamic 5-HT and plasma corticosterone by DICLO were noted which further justifies the above statement.

It is suggested that PGs may be involved in H-H-A axis activation during stress through the positive modulation of 5-HTergic system and PGs may also be involved in stress attenuating effect of Panax ginseng and diazepam.

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