ANTI-STRESS ACTIVITY OF RISPERIDONE, AN ATYPICAL ANTIPSYCHOTIC DRUG, IN RAT STRESS MODELS

Bhagawati Saxena¹, Sanjay Singh*¹

¹ Department of Pharmaceutics, Institute of Technology, Banaras Hindu University, Varanasi-221005 (U.P.), India

Summary

The present investigation was undertaken to explore the effect of risperidone on stress induced alteration in ulcer index, plasma levels of corticosterone, norepinephrine, glucose, cholesterol as well as adrenal gland weight. The anti-stress effect was evaluated against cold restraint stress, 4 h restraint stress, water immersion restraint stress and food deprived stress models. The rats (n=6) were randomly assigned to non-stressed control, stress control and treatment groups (risperidone 0.1, 0.3 and 1.0 mg/kg, p.o., for 21 days) in each stress model. Anti-stress effect of risperidone in each stress model was studied by ulcer scoring, weighing adrenal gland, estimation of plasma corticosterone, norepinephrine, glucose and total cholesterol levels using HPLC with PDA detector, fluorimetry and span diagnostic kits respectively. Results show that cold restraint stress, 4 h restraint stress, water immersion restraint stress and food deprivation stress increased ulcer index, corticosterone, norepinephrine, glucose and total cholesterol levels in plasma significantly. In contrast to above observation, no significant effect of stress on adrenal gland weight was found. 21 days repeated oral pretreatment with risperidone in all the stress models mitigated the stress induced increase in ulcer index, plasma levels of corticosterone, norepinephrine, glucose and total cholesterol. This study substantiates that the risperidone is effective in minimizing stress responses thereby beneficial in stress therapy.

Key words: Risperidone, stress, corticosterone, norepinephrine, glucose, cholesterol

*Corresponding Author:
Sanjay Singh
Professor of Pharmacology
Department of Pharmaceutics,
Institute of Technology,
Banaras Hindu University,
Varanasi-221005 (U.P.), India
E-mail address: drsanjaysingh@rediffmail.com,
ssingh.phe@itbhu.ac.in
Introduction

Now days, stress level perceived by people seem to have risen considerably. Stress results in increased incidences of several psychiatric disorders such as depression, anxiety, cognitive dysfunction, immunosuppression, diabetes, irritable bowel syndrome, male impotence, gastric ulcer, hypertension and ulcerative colitis (1). Stress can be defined as a non-specific response of the body to the demands enforced on it (2). The body responds to the stress by the way of allostasis or adaptation. Allostasis or adaptation is the process of continuous effort of the body to maintain normal physiological functions. The human body is well equipped to deal with stress. However, too much stress or inefficient management of allostasis leads to allostatic load which may precipitate disease and hence need to be treated (3). Thus, stress that is not resolved through coping or adaptation, deemed distress, may lead to mental disorders like anxiety and depression (4).

The hypothalamic–pituitary–adrenal (HPA) axis and the sympathoadrenal system (SAS) are the two main systems, which serve to maintain homeostasis (5). Activation of HPA axis to stress stimulates adrenal cortex to secrete corticosterone (5). On the other hand the autonomic response of SAS is responsible for fight-or-flight responses. The pathological conditions of stress occurred as a result of alterations in the above homeostatic processes (6). Bidirectional regulation of corticotrophin-releasing hormone (CRH) and norepinephrine (NE) systems is well established interaction of the central nervous system (CNS) and HPA axis. This interaction is mainly responsible for biological responses of organism to environmental challenges. Any derangement in the function of these systems would lead to the collapse of the stress responses and increase susceptibility of organism to stress disorders.

Prescriptions of anti-stress medications are generally comprised of antipsychotic drugs in addition to benzodiazepines and antidepressants. Risperidone is an atypical antipsychotic drug. It is a 5HT₂A and D₂ receptors antagonist and 5HT₁A receptor agonist. It has been reported that risperidone has anxiolytic activity (7) and certain anxiolytic drugs have shown to reduce gastric lesion produced due to stress in experimental models (8). Thus, risperidone may be potentially effective against stress. The present study investigated whether, risperidone being an atypical antipsychotic drug may act as anti-stress agent. This investigation further explores the effect of risperidone on stress induced changes of ulcer index, adrenal gland weight, plasma levels of corticosterone, norepinephrine, glucose and cholesterol in cold restraint stress, 4 h restraint stress, water immersion restraint stress and food deprivation stress models.

Materials and Methods

Drugs

Risperidone was obtained from APL Research center, Hyderabad, India as a gift sample. It was dissolved in 0.3% carboxymethylcellulose (CMC). All other chemicals, kits for estimation of biochemical parameters (glucose and cholesterol) and reagents of high-performance liquid chromatography (HPLC) were procured from local suppliers.
Animals

Adult male Wistar albino rats (180-220 g) were obtained from the Central Animal House, Institute of Medical Sciences, Banaras Hindu University (B.H.U.). The animals were housed in polypropylene cages at an ambient temperature of 25°C ± 1°C and 45-55% RH, with a 12:12 h light/dark cycle. The animals had free access to commercial food pellets (Doodh dhara Pashu Ahar, India) and water unless stated otherwise. Experiments were conducted between 09:00 and 14:00 h. “Principles of laboratory animal care” (NIH publication number 85-23, revised 1985) guidelines and standard operating procedures of CPCSEA issued by the Animal Welfare Division of Ministry of Environment and Forests, January 2010 were followed.

Preliminary study for selection of dose and treatment period of risperidone

The doses of risperidone (0.1, 0.3 and 1 mg/kg, p.o.) were used in accordance with Ishida-Tokuda et al (7). Rats (n=6) were randomly assigned to non-stress control, stress control and treatment groups. Treatment groups were treated with risperidone (0.1, 0.3 and 1.0 mg/kg, p.o.) for 1, 7, 14, 21 and 28 days repeatedly. Lastly, all the rats were exposed to 2 h of cold restraint stress (4-7°C) and their stomachs were taken out for ulcer scoring.

Experimental protocol

In cold restraint stress, 4 h restraint stress, water immersion restraint stress and food deprived stress models, rats were divided into five groups and each group comprises of 6 rats. The treatment period consisted of 21 days in all the models. The following doses of risperidone were administered in the respective groups:

Group I (Non stress control): 3 ml/kg of vehicle (0.3% Carboxymethylcellulose) (CMC), p.o.
Group II (Stress control): 3 ml/kg of vehicle (0.3% CMC), p.o.
Group III (RIS-0.1): Risperidone 0.1 mg/kg, p.o.
Group IV (RIS-0.3): Risperidone 0.3 mg/kg, p.o.
Group V (RIS-1.0): Risperidone 1.0 mg/kg, p.o.

Anti-stress effect of risperidone

1. Cold restraint stress model. The animals were fasted for 18 h before stress. One h after vehicle/risperidone treatment on 21st day the fore and hind limbs of rats were tied separately on wooden block with adhesive tape to immobilize them. Lastly, all the rats were subjected to the temperature of 4-7°C for 2 h. Blood was collected from all the animals for estimation of corticosterone, norepinephrine, glucose and total cholesterol. Animals were sacrificed after the experiment and their stomachs and adrenal glands were taken out for ulcer scoring and weighing respectively (9).

2. Restraint stress model. Animals were exposed to one stress session consisting of a 4 h restraint period (5x5x20 cm³ restrainer cages) at room temperature during the early phase of the light cycle after 18 h of fasting on 21st day, after 1 h of vehicle/risperidone administration. Blood was collected from all the animals for estimation of corticosterone, norepinephrine,
glucose and total cholesterol. Animals were sacrificed after the experiment and their stomachs and adrenal gland were taken out for ulcer scoring and weighing respectively (10).

3. Water immersion restraint stress model. The animals were fasted for 18 h before the stress. Caged sized (5×5×20 cm³) was used for inducing water immersion restraint stress. Immobilization was done by filling extra space using cotton and immersed vertically up to level of xyphoid in water bath (20-25°C). After 4 h of stress, the body was wiped dry, and the rats were then returned to their home cages. Blood was collected from all the animals for estimation of corticosterone, norepinephrine, glucose and total cholesterol. Lastly, all animals were sacrificed by cervical dislocation. Stomach was then dissected along the greater curvature and washed out with tap water to remove gastric content and blood clots and subjected to ulcer scoring. Adrenal glands were taken out from all the sacrificed rats for weighing (11).

4. Food deprivation stress. Different groups of rats were food deprived for a period of 5 days. Blood was collected from all the animals for estimation of corticosterone, norepinephrine, glucose and total cholesterol. Animals were then sacrificed by cervical dislocation. Stomach was then dissected along the greater curvature and washed with tap water to remove gastric content and blood clots and subjected to ulcer scoring. Adrenal glands were taken out for weighing (12).

Blood collection and glucose, cholesterol estimation

Blood was collected from retro-orbital plexus of all the rats under light halothane anesthesia using capillary tubes into micro centrifuge tubes containing heparin (10 µl, 1000 IU ml⁻¹). The plasma from the collected blood was separated by cold (4°C) centrifugation (5 min, 5000 rpm). Separated plasma was stored in -80°C till the day of biochemical estimation. Glucose and total cholesterol level in the plasma was estimated using span diagnostic kit.

Estimation of plasma corticosterone level

Corticosterone level in the separated plasma was estimated by HPLC/PDA system (Waters, USA), according to Woodward and Emery method (13). Dexamethasone was used as an internal standard. Briefly, 500 µl of plasma containing known quantity of dexamethasone was extracted with 5 ml of dichloromethane. The dichloromethane extract was evaporated to dryness and dissolved in 100 µl of mobile phase. 20 µl of extract was injected into HPLC system for quantification. Mobile phase consisted of methanol: water (70:30) at a flow rate of 1.0 mL/min and corticosterone was detected at 250 nm using PDA detector (Model 2998, Waters, USA). Water Spherisorb® C18 (250 mm × 4.6 mm, 5 µm) was used as analytical column. The chromatogram was recorded and analyzed with Empower software.

Estimation of norepinephrine

Norepinephrine was estimated using the fluorimetric method (14, 15). Briefly, the separated plasma was homogenized with cold n-butyl alcohol at a 1: 10 volume, shakes well for 5 min and centrifuged at 3000 rpm for 5 min. To the supernatant was added 5 ml of n–heptane and 0.1 M HCl. This mixture was vortexed for 5 min and then centrifuged at 3000 rpm for 5 min. The water phase contained norepinephrine. To 1 ml of the water phase was added phosphate saline buffer 1.7 ml (pH 7.2) and iodine reagent 0.1 ml and then allowed to stand for exactly 2 min, after which 0.5 ml of alkaline sodium sulfite solution was added. After 2 min, 0.6 ml
of 6 M glacial acetic acid was added. The mixture was boiled for 20 min, and the NE fluorescence was read at 385/475 nm after cooling.

Statistical analysis

The results were expressed as mean ± SEM. The data were analyzed with GraphPad Prism 4 (San Diego, CA, USA). Statistical significance was determined by one-way analysis of variance (ANOVA) followed by post hoc Tukey test. \( P<0.05 \) was considered to be statistically significant.

Results

Figure 1 of preliminary study shows that single pretreatment with all the doses of risperidone was ineffective against 2 h of cold restraint stress. Therefore, more prolonged treatment was done. We found that 21 days repeated pretreatment with risperidone was more effective than 7 and 14 days repeated treatment. Moreover, 28 days repeated pretreatment with risperidone did not lead to any further significant increase in the anti-stress activity. Therefore, 21 days treatment schedule was followed for the rest of the experiments in the present study.

![Figure 1](image-url)

Fig 1. Effect of 1 day, 7 days, 14 days, 21 days and 28 days repeated pretreatment with risperidone (0.1, 0.3 and 1.0 mg/kg) on ulcer index in CRS model. Results in each column are expressed as Mean ± SEM (n=6). \(*P<0.05\) and \(\text{@}P<0.05\) compared to control and stress group respectively (One way ANOVA followed by Tukey’s test).

Cold restraint stress, 4 h restraint stress, water immersion restraint stress and food deprived stress exposure increased the ulcer index, corticosterone, norepinephrine, glucose and total cholesterol levels in rats significantly (\( P<0.05 \)) while there is no significant difference on rats’s adrenal gland weight among the groups (Tables 1, 2, 3 and 4).

In cold restraint stress model, 21 days repeated risperidone pretreatment with the doses of 0.1, 0.3 and 1.0 mg/kg, p.o., were found effective in significantly (\( P<0.05 \)) reducing stress induced increased ulcer index, corticosterone, norepinephrine and glucose levels in plasma while only 0.1 and 0.3 mg/kg oral doses of risperidone were effective in reducing stress induced increased total cholesterol level (Table 1).
**Table No. 1.** Effect of 21 days repeated pretreatment with risperidone on ulcer Index, corticosterone, adrenal gland weight, glucose and total cholesterol in cold restraint stress (CRS) model.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Ulcer Index</th>
<th>Adrenal gland weight (mg/100g of Body weight)</th>
<th>Corticosterone (ng/ml)</th>
<th>Norepinephrine (µg/ml)</th>
<th>Glucose (mg/dl)</th>
<th>Total Cholesterol (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0 ± 0</td>
<td>14.09 ± 1.06</td>
<td>231.49 ± 22.53</td>
<td>36.42 ± 2.55</td>
<td>112.86 ± 2.56</td>
<td>62.05 ± 2.82</td>
</tr>
<tr>
<td>CRS</td>
<td>26 ± 1.59*</td>
<td>14.99 ± 0.95</td>
<td>799.34 ± 27.45*</td>
<td>68.43 ± 2.52</td>
<td>171.48 ± 4.17</td>
<td>97.27 ± 2.14</td>
</tr>
<tr>
<td>RIS-0.1</td>
<td>7.17 ± 0.60*</td>
<td>15.14 ± 0.86</td>
<td>461.26 ± 35.20*</td>
<td>36.00 ± 2.34</td>
<td>106.49 ± 4.87</td>
<td>66.67 ± 3.76</td>
</tr>
<tr>
<td>RIS-0.3</td>
<td>16.67 ± 1.12*</td>
<td>15.10 ± 0.88</td>
<td>629.98 ± 26.70*</td>
<td>48.36 ± 4.08</td>
<td>134.23 ± 2.56</td>
<td>82.91 ± 4.23</td>
</tr>
<tr>
<td>RIS-1.0</td>
<td>18.17 ± 1.56*</td>
<td>14.63 ± 1.23</td>
<td>691.61 ± 18.82*</td>
<td>58.34 ± 1.67</td>
<td>146.76 ± 3.94</td>
<td>90.09 ± 2.78</td>
</tr>
</tbody>
</table>

Results in each column are expressed as Mean ± SEM (n=6). *P< 0.05, †P< 0.05 and ‡P< 0.05 compared to control, CRS and RIS=0.1 respectively (One way ANOVA followed by Tukey’s test).

**Table No. 2.** Effect of 21 days repeated pretreatment with risperidone on ulcer Index, corticosterone, adrenal gland weight, glucose and total cholesterol in restraint stress (RS) model.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Ulcer Index</th>
<th>Adrenal weight (mg/100gm of Body weight)</th>
<th>Corticosterone (ng/ml)</th>
<th>NE (µg/ml)</th>
<th>Glucose (mg/dl)</th>
<th>Total Cholesterol (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0 ± 0</td>
<td>15.40 ± 1.54</td>
<td>246.03 ± 22.80</td>
<td>37.38 ± 2.34</td>
<td>125.84 ± 3.01</td>
<td>68.55 ± 2.82</td>
</tr>
<tr>
<td>RS</td>
<td>23.17 ± 0.54</td>
<td>16.86 ± 1.08</td>
<td>813.90 ± 26.80</td>
<td>70.44 ± 2.49</td>
<td>185.91 ± 6.29</td>
<td>102.39 ± 3.76</td>
</tr>
<tr>
<td>RIS-0.1</td>
<td>9.83 ± 1.05*</td>
<td>15.98 ± 1.88</td>
<td>476.82 ± 34.91*</td>
<td>38.39 ± 2.55</td>
<td>115.99 ± 4.87</td>
<td>71.80 ± 3.76</td>
</tr>
<tr>
<td>RIS-0.3</td>
<td>15.83 ± 1.40*</td>
<td>15.80 ± 1.11</td>
<td>647.88 ± 27.36*</td>
<td>50.34 ± 4.08</td>
<td>148.32 ± 2.54</td>
<td>88.03 ± 4.23</td>
</tr>
<tr>
<td>RIS-1.0</td>
<td>19.5 ± 1.5*</td>
<td>15.22 ± 1.12</td>
<td>726.17 ± 32.35*</td>
<td>66.98 ± 2.07</td>
<td>173.04 ± 6.09</td>
<td>95.21 ± 2.78</td>
</tr>
</tbody>
</table>

Results in each column are expressed as Mean ± SEM (n=6). *P< 0.05, †P< 0.05 and ‡P< 0.05 compared to control, RS and RIS-0.1 respectively (One way ANOVA followed by Tukey’s test).
In 4 h restraint stress only 0.1 and 0.3 mg/kg oral doses of risperidone for 21 days were effective in reducing stress induced increased ulcer index, corticosterone, norepinephrine, glucose, total cholesterol levels while 1.0 mg/kg dose of risperidone was found ineffective (Table 2).

**Table No. 3.** Effect of 21 days repeated pretreatment with risperidone on ulcer Index, corticosterone, adrenal gland weight, glucose and total cholesterol in water restraint stress (WRS) model

<table>
<thead>
<tr>
<th>Groups</th>
<th>Ulcer Index</th>
<th>Adrenal weight (mg/100gm of Body weight)</th>
<th>Corticosterone (ng/ml)</th>
<th>NE (µg/ml)</th>
<th>Glucose (mg/dl)</th>
<th>Total Cholesterol (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0 ± 0</td>
<td>14.40 ± 0.67</td>
<td>237.27 ± 10.63</td>
<td>43.29 ± 1.99</td>
<td>128.76 ± 3.64</td>
<td>67.66 ± 2.25</td>
</tr>
<tr>
<td>WRS</td>
<td>21.67 ± 1.25</td>
<td>15.41 ± 0.84</td>
<td>755.14 ± 42.06</td>
<td>67.05 ± 2.19</td>
<td>189.44 ± 6.60</td>
<td>94.36 ± 4.20</td>
</tr>
<tr>
<td>RIS-0.1</td>
<td>8.83 ± 1.14</td>
<td>15.99 ± 1.56</td>
<td>482.06 ± 31.45</td>
<td>35.16 ± 2.30</td>
<td>127.58 ± 7.33</td>
<td>67.33 ± 4.68</td>
</tr>
<tr>
<td>RIS-0.3</td>
<td>14.5 ± 1.88</td>
<td>15.21 ± 1.14</td>
<td>622.12 ± 17.45</td>
<td>41.75 ± 1.55</td>
<td>138.50 ± 12.78</td>
<td>72.97 ± 4.41</td>
</tr>
<tr>
<td>RIS-1.0</td>
<td>18.67 ± 1.43</td>
<td>15.05 ± 0.74</td>
<td>727.41 ± 32.35</td>
<td>59.42 ± 1.48</td>
<td>158.45 ± 10.27</td>
<td>80.59 ± 3.40</td>
</tr>
</tbody>
</table>

Results in each column are expressed as Mean ± SEM (n=6). *P < 0.05, †P < 0.05 and ‡P < 0.05 compared to control, WRS and RIS-0.1 respectively (One way ANOVA followed by Tukey’s test).

**Table No. 4.** Effect of 21 days repeated pretreatment with risperidone on ulcer Index, corticosterone, adrenal gland weight, glucose and total cholesterol in food deprived stress (FDS) model

<table>
<thead>
<tr>
<th>Groups</th>
<th>Ulcer Index</th>
<th>Adrenal Weight (mg/100gm of Body weight)</th>
<th>Corticosterone (ng/ml)</th>
<th>NE (µg/ml)</th>
<th>Glucose (mg/dl)</th>
<th>Total Cholesterol (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0 ± 0</td>
<td>14.83 ± 0.85</td>
<td>289.26 ± 10.63</td>
<td>44.03 ± 1.99</td>
<td>106.31 ± 2.83</td>
<td>54.30 ± 0.77</td>
</tr>
<tr>
<td>FDS</td>
<td>22.17 ± 1.64</td>
<td>15.99 ± 2.20</td>
<td>807.13 ± 42.06</td>
<td>67.80 ± 2.19</td>
<td>162.78 ± 5.91</td>
<td>80.34 ± 3.30</td>
</tr>
<tr>
<td>RIS-0.1</td>
<td>10.17 ± 1.52</td>
<td>15.61 ± 0.64</td>
<td>534.05 ± 31.45</td>
<td>35.90 ± 2.30</td>
<td>97.06 ± 4.08</td>
<td>59.12 ± 3.46</td>
</tr>
<tr>
<td>RIS-0.3</td>
<td>15.17 ± 1.52</td>
<td>15.81 ± 1.22</td>
<td>684.44 ± 31.45</td>
<td>42.49 ± 2.30</td>
<td>127.45 ± 4.08</td>
<td>63.54 ± 3.46</td>
</tr>
<tr>
<td>RIS-1.0</td>
<td>18.5 ± 1.67</td>
<td>15.87 ± 1.41</td>
<td>779.40 ± 32.35</td>
<td>60.16 ± 1.48</td>
<td>139.33 ± 3.73</td>
<td>69.53 ± 3.14</td>
</tr>
</tbody>
</table>

Results in each column are expressed as Mean ± SEM (n=6). *P < 0.05, †P < 0.05 and ‡P < 0.05 compared to control, FDS and RIS-0.1 respectively (One way ANOVA followed by Tukey’s test).
In water immersion restraint stress and food deprived stress models oral pretreatment with risperidone (0.1 and 0.3 mg/kg) for 21 days significantly \((P<0.05)\) decreased stress induced increase in ulcer index, corticosterone and total cholesterol levels. In the contrast all the doses of risperidone were found effective in decreasing stress induced increase in norepinephrine and glucose levels (Table 3 and 4). In this study risperidone showed inverse dose effect relationship in each stress model. This implies that risperidone is most effective at its lowest dose (0.1 mg/kg) and with increase in dose from 0.1 to 1.0 mg/kg its anti-stress activity decreased.

**Discussion**

In this investigation, risperidone pretreatment showed significant anti-stress activity in the cold restraint stress, 4 h restraint stress, water immersion restraint stress and food deprived stress models. Interestingly, risperidone showed an inverse-shaped dose–response relationship for its anti-stress effect in terms of reduction in ulcer index, corticosterone, norepinephrine, glucose and total cholesterol levels. However for the first time the anti-stress activity of risperidone is reported by its ability to reduce stress-induced SAS and HPA axis activation.

There are various models used for the assessment of anti-stress effect which include cold restraint stress, restraint stress, water immersion restraint stress, activity wheel stress, foot shock stress, food deprivation stress, sound stress and anorexic stress tolerance models. In this study, anti-stress activity of risperidone was evaluated against cold restraint stress, 4 h restraint stress, water immersion restraint stress and food deprivation stress models which create mild or acute stress with the activation of SAS and HPA axis.

Exposure of organism to any kind of stressor leads to the activation of SAS and HPA systems (16). Stimulation of SAS causes an increase in plasma norepinephrine level while activation of HPA systems intern increases the release of corticosterone from adrenal gland. Earlier it was reported that plasma corticosterone and NE levels are increased after acute immobilization stress (17). In addition to the release of corticosterone through activation of HPA axis, periventricular nucleus of hypothalamus in stress condition also causes decrease in gastric mucosal blood flow through efferent nerve fibers (18). This results in ischemia which leads to free radical generation. The resulted free radical causes oxidative damage and ultimately results in ulcer formation (19). Thus, gastric erosion as well as release of corticosterone and norepinephrine is some of the important outcomes of stress responses (17, 18). Result of present study shows that rats subjected to cold restraint stress, restraint stress, water immersion restraint stress and food deprivation stress showed significant increase in ulcer scoring, corticosterone and norepinephrine levels.

Stress induced increase in corticosterone and norepinephrine levels result in increase in glucose level. Corticosterone increase blood glucose by inducing glucose release from hepatocytes and inhibiting glucose uptake by cells through decreasing GLU-4 transporter, stimulating gluconeogenesis and glucagon secretion (20). Norepinephrine increase blood glucose level indirectly by inhibiting insulin release thereby decrease glucose uptake and increase in gluconeogenesis. Norepinephrine also increases growth hormone like ACTH which intern increases glucose level. In agreement to above statement, this study shows that all the stress models increased the blood glucose level. Stress induced increase in corticosterone causes immobilization of lipids and synthesis of cholesterol (21). Thus, rats
subjected to cold restraint stress, restraint stress, water immersion restraint stress and food deprivation stress showed significant increase in total cholesterol levels in plasma.

HPA axis is regulated by higher limbic brain regions. The major components of the stress reaction include activation of limbic (prefrontal cortex, hippocampus, and amygdala) and hypothalamic brain structures (22). It has also been suggested that high levels of 5HT$_{2A}$ receptor subtype in the prefrontal cortex area mediate stress in addition to emotion and cognition responses (23). Hippocampus contains 5HT$_{2A}$ receptor subtype (24) and involved in stress responses (25). Hippocampus regulates HPA axis in which activation of hippocampus due to stress stimulates adrenal cortex to secrete corticosterone (26). Additionally, it is reported that 5HT$_{2A}$ receptor involved in the progression of stress and release of corticosterone (27).

Results show that risperidone pretreatment decreased the stress induced increase in ulcer index, corticosterone, norepinephrine, glucose and total cholesterol levels. This can be due to the antagonistic activity of risperidone (RIS) on the brain hippocampal and prefrontal cortex 5HT$_{2A}$ receptors and thus it can modulate the downstream pathways associated with stress. However, results show that risperidone showed inverse dose effect relationship i.e., most effective at lowest dose (0.1 mg/kg) while further increasing the dose lead to decrease in the anti-stress effect in terms of decreasing stress induced increased ulcer index, corticosterone, norepinephrine, glucose and total cholesterol levels.

It is well known that chronic stress increases the adrenal gland weight due to hypertrophy to compensate the demand of corticosterone while acute stress increases the release of corticosterone due to the release of stored corticosterone in adrenal gland and thus does not alter the adrenal gland weight (28). Results of this study also show that cold restraint stress, restraint stress, water immersion restraint stress and food deprived stress causes the release of stored corticosterone in adrenal gland and hence did not increase adrenal gland weight as all the stress models used in this study are mild or acute.

**Conclusion**

Risperidone is found to be effective in minimizing stress responses maximum at the dose of 0.1 mg/kg than 0.3 and 1 mg/kg thereby beneficial in stress therapy.

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**Reference:**


