Antihypertensive effect of newly synthesized acyl amino substituted propanolamine derivatives, DPJ 890 and DPJ 955 in rats

Sir,

Hypertension described as a ‘silent killer’ increases the incidence of cardiovascular diseases. β blockers have been widely used since more than four decades for the treatment of hypertension. However these drugs are contraindicated in asthmatics and diabetics. In order to improve the therapeutic variety, Late D. P. Jindal (Panjab University) had synthesized new compounds for β blocking activity. The synthesis and adrenoreceptor (β₁ and β₂) binding affinities of these compounds were reported earlier. Previous work indicated that DPJ 890 and DPJ 955 possessed greater β₁ adrenoreceptor selectivity than standard β blocking drugs like atenolol and propranolol among various compounds synthesized from the series. As a collaborative research work we received compound DPJ 890 and DPJ 955, which are chemically N[4 - (3 – tert – butylamino – 2 – hydroxy – propoxy) – phenyl] – 3,4 – dimethoxy benzamide oxalate and N[5 - (3 – tert – butylamino – 2 – hydroxy – propoxy) – naphthalene-1-yl] – acetamide oxalate respectively for evaluating the antihypertensive potential.

Female Wistar rats (175-200 g) purchased from the National Toxicology Centre, Pune, India, were housed in a clean environment, at a temperature of 25±1°C and a relative humidity of 45 to 55%, under 12/12 h light/dark cycle. The animals had free access to food pellets (Chakan Oil Mills, Pune, India). The research protocol was approved by the Institutional Animal Ethics Committee (IAEC) of the Poona College of Pharmacy, Pune, India.

Two-kidney 1 clip model of kidney ligation was used to produce hypertension in rats. Group I animals had not undergone renal ligation. Rats were anesthetized with urethane (1.25 mg/kg, i.p.) and the left renal artery (LRA) was ligated except in Group I rats. After renal ligation the animals were housed and provided with 1% sodium chloride solution instead of water. After 6 weeks of LRA ligation the animals were divided into 9 groups consisting of 6 animals in each group. Group II received vehicle [saline (0.9% sodium chloride in water), 1 ml/kg, i.p.], which served as LRA ligated control. Groups III, IV, V, VI, VII and VIII received a dose of DPJ 955 (3, 10 or 30 mg/kg) or DPJ 890 (1, 3 or 10 mg/kg) intraperitoneally, respectively. Groups IX and X received standard drug propranolol (30 mg/kg, i.p.) and atenolol (10 mg/kg, i.p.) respectively. Saline or drug treatment was initiated after 6 weeks of LRA ligation and treatment was continued for 7 days. The mean arterial pressure (MAP) was recorded by directly cannulating the carotid artery using four-channel physiological data acquisition system (MP 30, BIOPAC Systems, Inc., Santa Barbara, CA). MAP was recorded at the end of the 7th week, 1 h after the administration of the last dose of saline or test drugs. The heart rate was computed from the ECG recording.

The statistical significance of the difference between means was determined using one-way analysis of variance followed by Tukey test. P<0.05 was considered significant. LRA ligation after 7 weeks had significantly (P<0.01) increased the MAP compared to non-ligated rats. However, the heart rate was not significantly changed as compared to non-ligated rats. Treatment with DPJ 890 (1, 3 and 10 mg/kg, i.p.) and DPJ 955

### Table 1

<table>
<thead>
<tr>
<th>Groups</th>
<th>Treatment (mg/kg, i.p)</th>
<th>Mean arterial blood pressure (mm/Hg)</th>
<th>Heart rate (beats/ min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Non-ligated*</td>
<td>90.5 ± 5.3</td>
<td>333.2 ± 4.2</td>
</tr>
<tr>
<td>II</td>
<td>LRA ligated control (saline 1 ml/kg)</td>
<td>198.5 ± 4.4**</td>
<td>327.5 ± 8.0</td>
</tr>
<tr>
<td>III</td>
<td>DPJ 955 (3)</td>
<td>177.0 ± 5.8</td>
<td>320.7 ± 8.0</td>
</tr>
<tr>
<td>IV</td>
<td>DPJ 955 (10)</td>
<td>157.0 ± 4.4*</td>
<td>314.3 ± 5.8</td>
</tr>
<tr>
<td>V</td>
<td>DPJ 955 (30)</td>
<td>150.3 ± 2.4**</td>
<td>293.0 ± 4.3*</td>
</tr>
<tr>
<td>VI</td>
<td>DPJ 890 (1)</td>
<td>172 ± 3.3*</td>
<td>319.3 ± 3.7</td>
</tr>
<tr>
<td>VII</td>
<td>DPJ 890 (3)</td>
<td>149.5 ± 4.9**</td>
<td>307.8 ± 5.9</td>
</tr>
<tr>
<td>VIII</td>
<td>DPJ 890 (10)</td>
<td>138.0 ± 4.9**</td>
<td>301.2 ± 7.8*</td>
</tr>
<tr>
<td>IX</td>
<td>Propranolol (30)</td>
<td>152.8 ± 4.2*</td>
<td>289.3 ± 5.3**</td>
</tr>
<tr>
<td>X</td>
<td>Atenolol (10)</td>
<td>147.5 ± 7.3**</td>
<td>297.3 ± 5.9*</td>
</tr>
</tbody>
</table>

One-way ANOVA

<table>
<thead>
<tr>
<th>F</th>
<th>df</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>33.91</td>
<td>59</td>
<td>0.64</td>
</tr>
</tbody>
</table>

*Animals in this group did not undergo left renal artery ligation and did not receive any treatment for a period of 7 weeks.
Values are expressed as means±SEM. *P<0.05, **P<0.01 as compared to LRA ligated control group. ***P<0.01 as compared to non-ligated rats.
(3. 10 and 30 mg/kg, i.p.) produced a significant, dose-dependent decrease in the MAP and heart rate of LRA ligated rats. Significant reduction in MAP and heart rate was observed in hypertensive rats treated with propranolol (30 mg/kg), atenolol (10 mg/kg), DPJ 890 (3 and 10 mg/kg) and DPJ 955 (10 and 30 mg/kg). The fall in the the MAP produced by DPJ 890 (10 mg/kg) was greater compared to atenolol and propranolol while the effect of DPJ 955 was less than that of atenol but greater than that of propranol (Table 1).

The observed change in the MAP and heart rate in LRA ligated rats with DPJ 890 may be due to its stronger receptor (β2) binding property compared to atenolol.

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References


Effect of curcumin on triton WR 1339 induced hypercholesterolemia in mice

Sir,

Curcumin (diferuloylmethane), a major component of turmeric, is a yellow pigment obtained from rhizomes of Curcuma longa, is commonly used in Indian cuisine as a spice and food-coloring agent. Curcumin and its analogues have a variety of physiological and pharmacological activities such as antioxidant, anti-inflamatory, and anticarcinogenic properties. The ability of curcumin to inhibit LDL oxidation and hypercholesterolemic effect in rabbits has been studied. Administration of curcumin to streptozotocin diabetic rats improves lipid profile. The ability of curcumin to decrease serum cholesterol, triglycerides and lipids has been studied extensively in various animal models by different authors. But the effect of curcumin on hyperlipidemia induced by triton WR 1339 (Tyloxapol: a nonionic detergent, oxyethylated tertiary octyl phenol formaldehyde polymer) has not yet been studied. In this model to study the hypolipidemic drugs, triton WR 1339 is administered i.v. or i.p. in rodents to produce hypercholesterolemia by accelerating hepatic cholesterol synthesis while in other models, hyperlipidemia is produced by feeding high cholesterol or high fat diet. Moreover Paoletti suggested the use of triton WR 1339 induced hyperlipidemia as an important approach to screen the action of hypolipidemic drugs. Hence in the present study, the effect of curcumin on serum triglycerides and total cholesterol was studied in triton WR 1339 induced hyperlipidemic mice.

The experiments and protocols described in present report were approved by the Institutional Animal Ethics Committee and are in accordance with guidance of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). The study was carried out in in-bred, male, Swiss albino mice (25 ± 4 g). All animals were housed in group of 6 and maintained under standardized condition (12/12 h light/dark cycle, 24° C) with free access to pellet food (CHAKKAN diet, Pranav Agro Pvt. Ltd., India) and water. Triton WR 1339 (Tyloxapol) was obtained from Sigma, St. Louis, MO, USA. Curcumin was obtained as a gift sample from Cherrain Chemicals Ltd., India. Curcumin was orally administered in 0.5% sodium carboxy methyl cellulose suspension. Hyperlipidemia was induced by single intravenous injection of 200 mg/kg of triton WR 1339 in normal saline. Control animals were injected with normal saline.

The animals were divided into following groups.

1. Control
2. Triton control
3. Triton treated + curcumin 100 mg/kg
4. Triton treated + curcumin 200 mg/kg
5. Triton treated + curcumin 400 mg/kg
6. Control treated with curcumin 400 mg/kg

Curcumin (100, 200 and 400 mg/kg) was orally administered, immediately as well as 24 h after triton injection. Mice were not fed but had free access to water during the experiment period (44 h). Forty four hours after triton injection, blood was collected from anaesthetized mice by cardiac puncture. Serum cholesterol and triglycerides were estimated using commercially available kits (SPAN Diagnostics Pvt. Ltd.).

The results are expressed as mean ± SEM. The difference between groups was analyzed by one-way analysis of variance (ANOVA) followed by Denett’s test with 5% level of significance (P<0.05). Percentage change was calculated using the formula % Change = [(ΔT - Tc) / Tc] x 100

Where ΔT = values of treated group and Tc = values of respective control group.

Total cholesterol and triglycerides levels were significantly increased in triton-injected animals as compared to control mice. Treatment with curcumin (100 mg/kg) caused 6.2% and 5.0% reduction in total cholesterol and triglycerides respectively. Treatment with (200 and 400 mg/kg) of curcumin caused a dose dependent change in total cholesterol and triglycerides (Table 1). Control mice treated with curcumin had no significant change in total cholesterol and triglycerides.