Effect of chronic clonidine treatment and its abrupt cessation on mean blood pressure of rats with a normal or an elevated blood pressure

J. ATKINSON, NICOLE BOILLAT, ROSELYNE PERA-BALLY, LISE PETERS-HAEFELI AND E. J. KIRCHERTZ

Institut de Pharmacologie de l'Université de Lausanne, Lausanne, Switzerland

(Received 31 October 1978; accepted 26 February 1979)

Summary

1. Clonidine (6 mg of base/1 of water) was given as drinking fluid to normotensive rats or rats with established or early hypertension.

2. Spontaneous hypertensive rats (6 months old: average dose of clonidine, 0.6 mg 24 h⁻¹ kg⁻¹) showed a sustained fall in blood pressure over 3 weeks.

3. The same clonidine solution given for 6 weeks to two-kidney Goldblatt rats with early-stage hypertension (average dose of clonidine: 1 mg 24 h⁻¹ kg⁻¹) or spontaneously hypertensive rats (clonidine dose: 1 mg) induced a fall in mean blood pressure, but no change in normotensive rats.

4. Replacement of clonidine by water induced hypertension and lability which led to death in hypertensive but not in normotensive rats.

Key words: antihypertensive agents, blood pressure, clonidine, withdrawal.

Introduction

Clonidine was introduced as an hypotensive agent in 1966. One year later, problems involved were described after abrupt cessation of chronic treatment (Hökfelt, Dymling & Hedeland, 1968). In several patients given clonidine at daily doses from 0.3 to 0.9 mg and for times varying from 6 to 30 days, abruptly stopping the treatment led to rebound hypertension and tachycardia with symptoms such as anxiety, headache and vomiting, accompanied by increased catecholamine excretion. Many reports of individual cases of withdrawal symptoms after abrupt cessation of clonidine have been published, but few publications (Hansson, Hunyor, Julius & Hoobler, 1973; Spach, Steimer & Bloch, 1977; Goldberg, Raftery & Wilkinson, 1977; Reid, Dargie, Davies, Wing, Hamilton & Dollery, 1977; Whitsett, Chrysant, Dillard & Anton, 1978) have described controlled clinical trials. Controversy has arisen, therefore, regarding the changes in blood pressure and heart rate after withdrawal of treatment. Blood pressure and heart rate may simply return to pretreatment values, at a faster rate than after cessation of other hypotensive treatment (Reid et al., 1977). Alternatively an actual overshoot of blood pressure and/or heart rate may occur. The overshoot idea has been described (Hansson et al., 1973), often on the basis of incomplete evidence such as pretreatment values. To resolve this problem of rebound hypertension, various attempts have been made to reproduce it in laboratory animals. Again conflicting results have been obtained (Cavero, Fenard, Finch, Lefevre & Roach, 1977; Dix & Johnson, 1977; Finch, Hicks & Dean, 1978; Oates, Stoker, McCarthy, Monaghan & Stokes, 1978a; Oates, Stoker, Monaghan & Stokes, 1978b). This is not surprising when one considers that investigations on the primary effect of clonidine, to cause a sustained fall in blood pressure, have also produced conflicting results in laboratory animals.

Correspondence: Dr J. Atkinson, Institut de Pharmacologie de l'Université de Lausanne, Rue du Bugnon 21, CH-1011 Lausanne, Switzerland.
We undertook this study in order to answer the following questions: (1) How does chronic clonidine treatment affect the blood pressure of normotensive and hypertensive rats? (2) On abrupt cessation of such chronic clonidine treatment is there simply a return of blood pressure to that of control animals not treated with clonidine, or an overshoot?

Materials and methods

Animals

Female rats were used in all experiments. In Expt. 1, 6 month old spontaneously hypertensive rats (Okamoto-Wistar strain), with established hypertension, were used; in Expt. 2, either normotensive rats (Wistar strain: Institut für Physiopathologie, University of Bern, Switzerland) or animals in the earliest phase of hypertension were used. The latter group consisted of young spontaneously hypertensive rats (age 38 days), or rats with Goldblatt-type hypertension of 1 day duration. Goldblatt-type one-clip hypertension was induced in 28 day old normotensive rats (Bern-Wistar strain) by placing a solid silver clip (gap diameter 0.2 mm) on the right renal artery and either removing the left kidney (one-kidney Goldblatt hypertension) or leaving it in place (two-kidney Goldblatt hypertension). These rats were given clonidine from the day after the constriction of the renal artery onwards.

Experimental procedures

Expt. 1: effect of chronic clonidine treatment in rats with established hypertension. A polyethylene cannula was placed in the dorsal aorta under light ether anaesthesia (Weeks, 1971) of ten adult female spontaneously hypertensive rats. The operation lasted 20 min and after it rats were given food and water ad libitum for a period of 5 days. On the sixth day they were split into two groups. The first (n = 6) group was given a solution of clonidine hydrochloride in water (6 mg of clonidine base/1) to drink, and the second (n = 4) was given water. Rats were individually housed and given food and fluid ad libitum. Mean blood pressure (mmHg, via the aortic cannula of a conscious, unstressed rat), as well as food and fluid intake, and body weight were measured every second day. The rats were killed at the end of 21 days of this regimen; no attempt was made to follow changes in blood pressure after withdrawal of clonidine.

Expt. 2: effect of chronic clonidine treatment and its abrupt withdrawal in normotensive rats or rats with developing hypertension. Each of four groups of rats (spontaneously hypertensive rats, one-kidney Goldblatt hypertensive rats, two-kidney Goldblatt hypertensive rats and normotensive rats) was split into two subgroups. The first subgroup was given water to drink (control group), and the second subgroup the same solution of clonidine as used in Expt. 1. Rats were communally housed and received food and fluid ad libitum. Food and fluid intake and body weight were measured every 3 or 4 days for the duration of the experiment (up to 6 weeks).

At the end of 5–6 weeks of this regimen, the drinking bottles were removed at 09.00 hours and the dorsal aorta was cannulated between 10.00 and 13.00 hours. No rat was cannulated later in the day than 13.00 hours. Immediately after the operation, the rat was returned to its home cage and its drinking bottle reinstalled. Rats previously drinking clonidine solution were now given water to drink, and rats previously given water were continued on water. Mean blood pressure was recorded immediately upon cannulation and, thereafter, continuously either up to death of the rat or for the next 24 h.

Heart and kidneys were removed and weighed, either (1) on spontaneous death after the hypertensive crisis after the change from clonidine to water, or (2) after killing by a blow on the head. 'Starting' blood pressure (Table 3), i.e. mean blood pressure before appearance of clonidine-withdrawal syndrome, was taken as a graphic average (a horizontal line judged by eye to be an average of the pressure peaks and valleys) of 1 h of slow-speed recording (chart speed: 0.025 mm/s) starting 1 h after recovery of the righting reflex (after ether anaesthesia used for aortic cannulation) and finishing 1 h later. Mean blood pressure lability indices [lability index = (standard deviation/average pressure) x 100; Synder, Nathan & Reis, 1978] were determined at two periods (11.00–16.00 hours after recovery from anaesthesia but before start of hypertensive crisis, see below, and 17.00–19.00 hours just before the first sustained rise in mean blood pressure in the hypertensive crisis) and were calculated as follows: mean blood pressures (to the nearest 2.5 mmHg) were taken every 45 s for 1 h of recording; the average and SD of the 90 values so obtained were used to calculate the lability index.
Clonidine: antihypertensive effect and withdrawal

Drugs used

Clonidine hydrochloride (Catapres) was kindly donated by C. H. Boehringer Sohn, A.G., Ingelheim, F.R.G.

Statistics

Results are given as mean ± SEM and comparisons between means were carried out by paired or unpaired t-tests.

Results

Expt. 1: effect of chronic clonidine treatment in rats with established hypertension

The female spontaneously hypertensive rats had a starting body weight of 218 ± 5 g (n = 10, mean for both subgroups). At the end of the 21 day experimental period, the clonidine-treated subgroup (220 ± 4 g) had an average body weight similar to that of the water-treated subgroup (206 ± 10 g). Drinking clonidine initially, slightly (but not significantly) depressed food intake. Food intake recovered by the seventh day.

There was a similar, initial decrease in fluid intake (on the fourth day: clonidine subgroup: 19 ± 1 ml/24 h per rat compared with the water subgroup: 24 ± 2, P < 0.05) but the consumption of clonidine solution later recovered and overtook that of water (end of period: 24 ± 1 vs 20 ± 1, P < 0.05). The average dose of clonidine at the end of the experimental period was 0.6 mg 24 h⁻¹ kg⁻¹.

Drinking clonidine significantly lowered heart rate (day 12: clonidine subgroup: 445 ± 6 beats/min; water subgroup: 471 ± 7, P < 0.05). Although heart rate was lower in the clonidine subgroup at the end of the experiment, the effect was no longer of statistical significance.

The ten rats had an initial mean blood pressure of 179 ± 6 mmHg. Drinking clonidine solution produced a 63 mmHg fall on day 4 (clonidine subgroup: 140 ± 10 vs 203 ± 5 mmHg for rats drinking water, P < 0.05). The difference in blood pressure decreased thereafter but a 42 mmHg difference (P < 0.05) was maintained at the end of the experiment.

In parallel to the experiment described above one-kidney Goldblatt hypertensive rats and two-kidney Goldblatt hypertensive rats (clips on renal artery 2 months before exposure to clonidine) bearing aortic cannulae were given the same clonidine solution to drink. By the fourth day mean blood pressure had significantly fallen to 90% of the value of controls (drinking water), but this effect was not maintained. All one-kidney Goldblatt hypertensive rats and two-kidney Goldblatt hypertensive rats drinking clonidine solution died within 1 week of starting the clonidine treatment, however, and so this experiment is not reported in full.

Having established that this clonidine solution would produce a sustained blood pressure-lowering effect in spontaneously hypertensive rats with established hypertension, we then investigated the effects of drinking such a solution (and its abrupt substitution by water) on the blood pressure of normotensive rats and animals with incipient hypertension.

Expt. 2: effect of chronic clonidine treatment and its abrupt withdrawal in normotensive rats or rats with early hypertension

Clonidine at the doses ingested killed rats in all groups: spontaneously hypertensive rats, 70% mortality; one-kidney Goldblatt hypertensive rats, 100%; two-kidney Goldblatt hypertensive rats, 45%; normotensive rats, 13%. As all one-kidney Goldblatt hypertensive rats died within 1 week of drinking clonidine solution, this group will be left out of the following discussion. The survivors grew more slowly than controls (Table 1). As in Expt. 1,

Table 1. Experiment 2: body weight and age at start and finish of clonidine solution or water drinking 5–6 weeks period

<table>
<thead>
<tr>
<th>Rats</th>
<th>Drinking fluid</th>
<th>Start n</th>
<th>Body wt. (g)</th>
<th>Age (days)</th>
<th>Finish n</th>
<th>Body wt. (g)</th>
<th>Time on treatment (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneously hypertensive</td>
<td>Clonidine</td>
<td>20</td>
<td>69 ± 1</td>
<td>38</td>
<td>6</td>
<td>113 ± 5</td>
<td>42 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>Water</td>
<td>15</td>
<td>71 ± 1</td>
<td>38</td>
<td>14</td>
<td>152 ± 3</td>
<td>45 ± 0.3</td>
</tr>
<tr>
<td>Two-kidney Goldblatt hypertensive</td>
<td>Clonidine</td>
<td>40</td>
<td>90 ± 2</td>
<td>29</td>
<td>22</td>
<td>186 ± 6</td>
<td>42 ± 2</td>
</tr>
<tr>
<td></td>
<td>Water</td>
<td>13</td>
<td>87 ± 4</td>
<td>29</td>
<td>13</td>
<td>200 ± 0.4</td>
<td>36 ± 0.2</td>
</tr>
<tr>
<td>Normotensive</td>
<td>Clonidine</td>
<td>15</td>
<td>98 ± 3</td>
<td>29</td>
<td>13</td>
<td>197 ± 4</td>
<td>39 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>Water</td>
<td>10</td>
<td>98 ± 4</td>
<td>29</td>
<td>10</td>
<td>217 ± 7</td>
<td>40 ± 3</td>
</tr>
</tbody>
</table>
TABLE 2. Experiment 2: mean food and fluid consumption in the first and third weeks of clonidine solution or water drinking 5–6 week period

The probability of significance of differences between means is based on independent means t-test: clonidine subgroup vs water subgroup within spontaneously hypertensive rats, two-kidney Goldblatt hypertensive rats or normotensive rats. Only significant differences are indicated: *P < 0.05; **P < 0.01.

<table>
<thead>
<tr>
<th>Rats</th>
<th>Drinking fluid</th>
<th>Fluid consumption (ml 24h⁻¹ kg⁻¹ body wt.)</th>
<th>Food consumption (g 24h⁻¹ kg⁻¹ body wt.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Week 1</td>
<td>Week 3</td>
</tr>
<tr>
<td>Spontaneously</td>
<td>Clonidine</td>
<td>95 ± 28</td>
<td>163 ± 2*</td>
</tr>
<tr>
<td>hypertensive</td>
<td>Water</td>
<td>132 ± 5</td>
<td>133 ± 10*</td>
</tr>
<tr>
<td>Two-kidney Goldblatt</td>
<td>Clonidine</td>
<td>103 ± 13</td>
<td>160 ± 2</td>
</tr>
<tr>
<td>hypertensive</td>
<td>Water</td>
<td>156 ± 24</td>
<td>177 ± 10</td>
</tr>
<tr>
<td>Normotensive</td>
<td>Clonidine</td>
<td>90 ± 6*</td>
<td>140 ± 5*</td>
</tr>
<tr>
<td></td>
<td>Water</td>
<td>156 ± 25*</td>
<td>120 ± 6*</td>
</tr>
</tbody>
</table>

Table 3. Experiment 2: final heart and kidney weights and mean blood pressure

Organs were removed either (a) on spontaneous death after the hypertensive crisis occurring during the 24 h after the change from clonidine to water, or (b) at autopsy 24 h after aortic cannulation with or without change in drinking fluid. Mean blood pressure is the graphic average of 1 h of slow-speed recording, starting 1 h after recovery of righting reflex (after ether anesthesia used for aortic cannulation) and finishing 1 h later (during the period 11.00–14.00 hours). The probability of significance of differences between means is based on independent means t-test: (a) clonidine-water vs water-water within spontaneously hypertensive rats, two-kidney Goldblatt hypertensive rats or normotensive rats; (b) normotensive/water-water subgroup rats vs two-kidney Goldblatt hypertensive/water-water subgroup rats or spontaneously hypertensive/water-water subgroup rats. Only significant differences are indicated: *P < 0.05; **P < 0.01; ***P < 0.001.

<table>
<thead>
<tr>
<th>Rats</th>
<th>Drinking fluids</th>
<th>n</th>
<th>Heart wt. (mg/kg) Left</th>
<th>Kidney wt. (mg/kg)</th>
<th>Mean blood pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneously</td>
<td>Clonidine</td>
<td>6</td>
<td>4258 ± 223</td>
<td>4824 ± 171</td>
<td>4311 ± 154</td>
</tr>
<tr>
<td>hypertensive</td>
<td>Water</td>
<td>14</td>
<td>4826 ± 213</td>
<td>4691 ± 418</td>
<td>4415 ± 320</td>
</tr>
<tr>
<td>Two-kidney Goldblatt</td>
<td>Clonidine</td>
<td>22</td>
<td>3942 ± 211</td>
<td>3675 ± 175</td>
<td>3387 ± 224</td>
</tr>
<tr>
<td>hypertensive</td>
<td>Water</td>
<td>13</td>
<td>4575 ± 339</td>
<td>5028 ± 382**</td>
<td>3256 ± 136</td>
</tr>
<tr>
<td>Normotensive</td>
<td>Clonidine</td>
<td>13</td>
<td>3267 ± 107**</td>
<td>3145 ± 100</td>
<td>3151 ± 117</td>
</tr>
<tr>
<td></td>
<td>Water</td>
<td>10</td>
<td>3439 ± 154</td>
<td>3598 ± 244</td>
<td>3439 ± 154</td>
</tr>
</tbody>
</table>

rats which died after drinking clonidine solution showed no external or internal gross pathological changes except for a constant fall in body weight.

The presence of clonidine in water lowered both food and fluid intake (Table 2), which increased by the third week to levels equal to or above those of rats drinking only water. As rats were housed communally, it is impossible to decide whether the increase in consumption was due to the development of tolerance to the effects of clonidine (Atkinson, Kirchertz & Peters-Haefeli, 1978b) or, more simply, to 'selection' of consumers, the non-consumers dying out. Most of the deaths occurred in the first week. Clonidine doses (µg 24 h⁻¹ kg⁻¹) based on fluid-consumption figures for the third week were: spontaneously hypertensive, 978; two-kidney Goldblatt hypertensive, 960; normotensive rats, 840.

Rats with both types of hypertension showed cardiac hypertrophy when compared with normotensive rats of the same age (Table 3). The hearts of rats treated with clonidine were lighter, but not significantly so, than those of rats given water to drink. Spontaneously hypertensive had heavier kidneys than normotensive rats and this was unaltered by drinking clonidine solution. Two-kidney Goldblatt hypertensive rats showed compensatory hypertrophy of the left kidney, the artery of which was not constricted, and this was abolished by drinking clonidine. In both spontaneously hypertensive and two-kidney Goldblatt hypertensive rats, mean blood pressure was significantly lowered in rats treated with clonidine (Table 3) to a level, in spontaneously hypertensive rats treated with clonidine, similar to normotensive values. Treatment with clonidine had no effect on the mean blood pressure of normotensive rats (Table 3). In this second experiment, damping by
Clonidine: antihypertensive effect and withdrawal

Fig. 1. Experiment 2: evolution of mean blood pressure after aorta cannulation in two rats with established spontaneous hypertension, one animal drinking clonidine followed by water (——), the other drinking water followed by water (---). Drinking bottles were removed at 09.00 hours; the rats were cannulated between 10.00 and 11.00 hours and the drinking bottles were replaced at 11.00 hours. Mean blood pressure is plotted as a percentage of 'starting' value, i.e. that taken between the first and second hours recovery from ether anaesthesia. Times are hours during the day of, and the day after cannulation.

The thin-bore cannula was such that pulse pressure and hence heart rate could not be reliably recorded.

An example of the changes in mean blood pressure occurring in spontaneously hypertensive rats during the 24 h after replacement of clonidine solution by water, is given in Fig. 1. All six, surviving spontaneously hypertensive/clonidine–water subgroup rats showed a hypertensive crisis, which was defined as follows: mean blood pressure rose (starting in the late afternoon) to a first sustained peak of 178 ± 9 mmHg by 298 ± 52 min after 13.00 hours, i.e. 9 h after the time when clonidine solution was last available. It should be noted that 13.00 hours, the final time for cannulations, was taken as reference time. Mean blood pressure then fell back to (or below) the starting value given in Table 3, only to rise again three or four times during the next 208 ± 51 min (up to 21.26 hours). Mean blood pressure fell to very low values (50 mmHg), which heralded death.

Mean blood pressure as the average of 90 individual measurements taken over a 1 h period (between 11.00 and 13.00 hours) was 125 ± 5 mmHg and the lability index 4.58 ± 0.79 (n = 6). Corresponding figures for the spontaneously hypertensive rats: water–water subgroup, 144 ± 3 and 3.91 ± 0.66 (n = 14). Average mean blood pressure rose in the spontaneously hypertensive rats: clonidine–water subgroup to 149 ± 4 mmHg (1 h period between 17.00 and 19.00 hours, P < 0.001 paired means t-test); the lability index also increased: 7.43 ± 1.31 (P < 0.01 paired means t-test). In contrast to the relatively long-lived peaks in mean blood pressure described above, an increase in lability index reflected the appearance (or intensification) of short-lived peaks (<2 min) of mean blood pressure.

All six surviving spontaneously hypertensive/clonidine–water subgroup rats showed such a crisis and all six died 769 ± 166 min after 13.00 hours, i.e. at 01.49 hours the following day. Gross autopsy revealed no obvious cause of death. In the 14 surviving spontaneously hypertensive/water–water subgroup rats, as indicated above by lability indices, mean blood pressure hovered around the values given in Table 3 with deviations of ± 20 mmHg. Of the 22 two-kidney Goldblatt hypertensive/clonidine–water subgroup rats surviving, seven showed a hypertensive crisis, reaching peak mean blood pressures of 186 ± 4 mmHg, with the first peak occurring 437 ± 188 min after 13.00 hours (20.17 hours). Mean blood pressure then fell and rose again three or four times during a period of 219 ± 66 min (up to 23.56 hours). Five of these
seven died after a hypotensive period as above at 886 ± 170 min after 13.00 hours (i.e. at 03.46 hours the following day). The remaining two rats showing a hypertensive crisis stabilized their mean blood pressure after 23.56 hours at values similar to the starting values given in Table 3. The 15 two-kidney Goldblatt hypertensive/water subgroup rats that did not show a hypertensive crisis had mean blood pressure which hovered within ±20 mmHg limits of the starting blood pressure for the whole 24 h recording period, as did the 13 surviving two-kidney Goldblatt hypertensive/water–water subgroup rats.

Of the 13 normotensive/clonidine–water subgroup rats surviving, five showed a hypertensive crisis [peak mean blood pressure values: 179 ± 7 mmHg; first peak: 572 ± 114 min after 13.00 hours (i.e. at 22.32 hours), peak activity lasting 272 ± 48 min up to 03.04 hours], but none died. In these five rats mean blood pressure stabilized after 03.04 hours at values similar to the starting values. The eight normotensive/clonidine–water subgroup rats not showing a hypertensive crisis (and the 10 normotensive/water–water subgroup rats) hovered within ±10 mmHg of the starting blood pressure for the whole 24 h period.

Discussion

Effect of chronic treatment with clonidine

Contradictory results have been published on changes in blood pressure in rats treated chronically with clonidine. Walland (1968) showed that clonidine given orally for 12 days produced an increase in blood pressure. In contrast to this, Laverty & Taylor (1969) reported an initial decrease in blood pressure (which was not maintained as tolerance to the hypotensive effect developed by day 14). Sugimoto, Hashida & Kasahara (1976), however, produced a blood pressure decrease which was sustained over 350 days. Likewise, Caverò et al. (1977) and Dix & Johnson (1977) produced sustained falls in blood pressure, but with much shorter treatment periods.

In our Expt. 1, clonidine given in the drinking fluid to spontaneously hypertensive rats for 21 days produced an initial fall in blood pressure and heart rate. Tolerance developed, but a significant 42 mmHg difference in blood pressure remained on day 21, although heart-rate values at this stage did not significantly differ from those of controls. We conclude that (1) in hypertensive rats chronic treatment with clonidine lowered blood pressure, and (2) tolerance to the cardiovascular effects developed. Tolerance to the anorexic effect (Atkinson et al., 1978b), and to a behavioural depressant effect (Meyer, El-Azhary, Bierer, Hanson, Robbins & Sparber, 1977), have been reported. In both instances, tolerance developed within a few days of chronic treatment.

An interesting finding was the high mortality of rats drinking clonidine solution and the relative susceptibilities of different rats: one-kidney Goldblatt hypertensive > two-kidney Goldblatt hypertensive + spontaneously hypertensive > normotensive rats. An adipsic effect may be implicated as it has been shown that clonidine solutions have an aversive taste for rats and, on first exposure, fluid and food intakes fall to very low levels (Atkinson, Kirchertz & Peters-Haefeli, 1977). A cardiovascular effect may be also implicated although it would seem unlikely that the rats died from complications of hypotension as at no stage did chronic clonidine treatment produce blood pressure values lower than normal (115–120 mmHg). However, rats may have drunk some clonidine solution, stopped abruptly because of its aversive taste and died from a self-imposed hypertensive withdrawal crisis.

Effect of abrupt cessation of chronic treatment with clonidine

There are few, highly contradictory, reports of withdrawal syndrome upon cessation of chronic clonidine treatment in animals. Dix & Johnson (1977) reported that on cessation of a 3 week period of clonidine consumption, the blood pressure of normotensive rats returned to control values with no rebound, whereas heart rate and adrenal tyrosine hydroxylase activity were significantly elevated. Likewise, Caverò et al. (1977) failed to produce hypertensive rebound in rats (but were able to produce it in cats and dogs). It may be that both groups cited above looked at periods before or after hypertensive rebound, since (1) on the basis of present experiments the phenomenon appears to be short-lived, and (2) on the basis of the reports of Oates et al. (1978a) and Prop (1978) (both of whom observed hypertensive rebound in rats) it occurs at a well-defined time (25 h after the last administration in both reports).

Although Prop (1978) and Finch et al. (1978) reported that the degree of hypertensive rebound was related to the dose of clonidine, Oates et al. (1978b) found no connection between clonidine
dose or duration of treatment and severity of blood pressure rebound on withdrawal.

On the basis of our results we conclude that on withdrawal of relatively long-term treatment with high oral doses of clonidine, given to young normotensive or developing hypertensive rats, a hypertensive crisis does occur. A hypothesis for its mechanism can be proposed. The increase in mean blood pressure lability seen in spontaneously hypertensive rats on withdrawal of clonidine in Expt. 2 is of the same order as that produced in the rat by selective destruction by injections of 6-hydroxydopamine of the catecholamine innervation of the nucleus tractus solitarii (Snyder et al. 1978). Chronic clonidine treatment may desensitize α-adrenoreceptors in the nucleus tractus solitarii to the effect of endogenous noradrenaline, such that the removal of the exogenous transmitter (clonidine) leaves the animal with a reduced capacity to modulate baroreceptor reflexes, which, in turn, provokes a withdrawal rebound and increases mean blood pressure lability. Snyder et al. (1978) also reported that high doses of 6-hydroxydopamine injected into the nucleus tractus solitarii produced 2–4 h of sustained hypertension, which was followed by a rapid fall of blood pressure, pulmonary oedema and death. Although there were no gross signs of pulmonary oedema, histological studies may reveal that the rats which died after the hypertensive crisis (in Expt. 2) followed a similar course.

Acknowledgments

The authors thank Professor G. Peters for his helpful advice. This work was supported by Swiss National Foundation grant 3.028.76 and was presented as a preliminary communication at the Seventh International Congress of Pharmacology, Paris (Atkinson, Kirchert & Peters-Haefeli, 1978a).

References


