ABSTRACT
Previous studies have shown that the immunosuppressant drug cyclosporine A attenuates arterial baroreceptor function. This study investigated whether the modulatory effect of cyclosporine on baroreceptor function involves inhibition of the baroreflex-facilitatory effect of testosterone. The role of cardiac autonomic control in cyclosporine-testosterone baroreflex interaction was also investigated. Baroreflex curves relating bradycardic responses to increments in blood pressure evoked by phenylephrine were constructed in conscious, sham-operated, castrated rats and in testosterone-replaced castrated (CAS + T) rats in the absence and presence of cyclosporine. The slopes of the curves were taken as an index of the baroreflex sensitivity (BRS). Short-term (11–13 days) cyclosporine treatment or castration reduced plasma testosterone levels and caused similar attenuation of the reflex bradycardia, as indicated by the significantly smaller BRS compared with sham-operated values (−0.97 ± 0.07, −0.86 ± 0.06, and −1.47 ± 0.10 beats/min/mm Hg, respectively). The notion that androgens facilitate baroreflexes is further confirmed by the observation that testosterone replacement of castrated rats restored plasma testosterone and BRS to sham-operated levels. Cyclosporine had no effect on BRS in castrated rats but caused a significant reduction in CAS + T rats. Muscarinic blockade by atropine caused approximately 60% reduction in the BRS in sham-operated rats, an effect that was significantly and similarly diminished by castration, cyclosporine, or their combination. β-Adrenergic blockade by propranolol caused no significant changes in BRS. These findings suggest that cyclosporine attenuates baroreflex responsiveness via, at least partly, inhibition of the testosterone-induced facilitation of cardiomotor vagal control.

Cyclosporine A is a potent immunosuppressant agent used in organ transplantation to prolong the survival of allogenic grafts and in the treatment of autoimmune diseases (Cohen et al., 1984). However, the clinical use of cyclosporine is often associated with serious cardiovascular disorders such as hypertension (Schachter, 1988; Scherrer et al., 1990). Several mechanisms have been proposed to explain the hypertensive effect of cyclosporine such as sympathetic activation (Scherrer et al., 1990; Chiu et al., 1992), direct vasoconstriction (Xue et al., 1987), and/or endothelin release (Kon et al., 1990). Attenuation of arterial baroreceptor responsiveness is another mechanism that may contribute to cyclosporine-induced hypertension. Gerhardt et al. (1999) have shown that cyclosporine elevates blood pressure in kidney transplant recipients, and this effect was associated with a reduced baroreflex function. Cyclosporine has also been shown to shift the midranges of baroreflex control of sympathetic nerve activity and heart rate to higher arterial pressures (Ryuzaki et al., 1997). Spectral analysis of the arterial pressure-heart period relationship in patients with heart transplantation showed that cyclosporine reduces the overall gain of baroreflex responsiveness to orthostatic stimulus (Lucini et al., 2000). Notably, the attenuation of baroreflex responsiveness is considered as an important independent risk factor for cardiac mortality (Schwartz et al., 1984; Tsuji et al., 1994).

The exact mechanism by which cyclosporine attenuates the baroreflex function, and whether it involves central or peripheral pathways, is not clear. It has been suggested that an imbalance between the sympathetic and parasympathetic activities due to an enhanced sympathetic tone may explain cyclosporine-induced baroreflex dysfunction (Gerhardt et al., 1999). Cyclosporine increases the production of thromboxane A2 and disturbs the prostaglandin (prostaglandin I2 and thromboxane A2) balance (Perico et al., 1986). Given that prostaglandin I2 increases the baroreceptor sensitivity (Chen et al., 1990), the altered prostaglandin profile may result in reduced baroreceptor sensitivity.

Reported findings have shown that cyclosporine causes testicular dysfunction. Cyclosporine produces dose-dependent reductions in serum testosterone levels and intratesticular testosterone contents (Krueger et al., 1991; Bowman et al., 1997), and impairs spermatogenesis (Srinivas et al., 1998). The alterations in testicular function by cyclosporine...
can be reversed by testosterone replacement therapy (Seethalakshmi et al., 1990). Interestingly, testosterone has been shown in a recent study from our laboratory to selectively modulate the baroreceptor control of reflex bradycardia versus no effect on reflex tachycardia (El-Mas et al., 2001). In the latter study, we provided the first experimental evidence that testosterone facilitates baroreflex function through a mechanism that involves enhancement of cardiac vagal activity. With this idea in mind, the ability of cyclosporine to reduce baroreflex responsiveness and serum testosterone levels raises the possibility that these two effects of cyclosporine are correlated. This assumption has not yet been investigated.

The present study, therefore, addressed two important questions pertinent to the hypothesis that testosterone modulates cyclosporine-induced baroreflex impairment: first, whether cyclosporine reduces baroreceptor responsiveness via inhibition of the facilitatory effect of testosterone on baroreflexes; and second, whether alterations in the cardiac autonomic control contribute to cyclosporine-testosterone baroreflex interaction. To accomplish these goals, baroreflex curves relating reflex HR responses to increments in blood pressure evoked by phenylephrine were established in conscious, freely moving, sham-operated, castrated rats and in CAS + T rats treated with cyclosporine or vehicle. Baroreflex responsiveness was measured in the absence and presence of atropine (muscarinic blocker) or propranolol (β-adrenergic blocker) to evaluate the roles of cardiac vagal and sympathetic activity, respectively, in the HR responses. The slopes of the curves were taken as an index of BRS. Plasma testosterone levels were also measured and correlated to changes in BRS.

Materials and Methods

Male Wistar rats (230–280 g; High Institute of Public Health, Alexandria, Egypt) were purchased from commercial vendors. Cyclosporine A (Sigma-Aldrich, St. Louis, MO), thiopental (Biochemie GmbH, Vienna, Austria), povidone-iodine solution (Betadine; Nile Pharmaceutical Co., Cairo, Egypt), and Penicillin (Cid Pharmaceutical Co., Cairo, Egypt) were purchased from commercial vendors. Cyclosporine A was a gift from Novartis Pharma, AG (Basel, Switzerland). A fresh solution of cyclosporine in sesame oil was prepared every 3 days and kept in the refrigerator.
**Statistical Analysis.** Values are expressed as mean ± S.E.M. The relationship between increases in MAP and associated decreases in HR was assessed by regression analysis for individual animals as described in our previous studies (El-Mas and Abdel-Rahman, 1992, 1998; El-Mas et al., 2001). The regression coefficient (slope of the regression line) expressed as beats per minute per mm Hg was taken as an index of BRS. Analysis of variance (ANOVA) followed by a Newman-Keuls post hoc analysis was used for multiple comparisons with the level of significance set at P < 0.05.

**Results**

**Cyclosporine-Testosterone Baroreflex Interaction.** The baseline values of MAP measured in conscious, freely moving rats on the day of the experiment were similar in all groups of rats (Table 1). The baseline HR values were not altered by castration or testosterone replacement, whereas they were significantly (P < 0.05) increased in cyclosporine-treated groups (CyA, CAS + CyA, and CAS + CyA + T) compared with sham-operated values (Table 1). Pooled data obtained prior to atropine or propranolol administration showed that i.v. administration of phenylephrine (0.5–8 μg/kg) produced dose-related increases in MAP that were associated with reflex decreases in HR (Table 2).

Multiple comparisons (ANOVA) of the mean pressor responses to phenylephrine revealed that these responses were not affected by short-term castration but showed significant (P < 0.05; ANOVA) reductions by cyclosporine treatment (20 mg/kg/day for 11–13 days) compared with sham-operated values (Table 2). The reflex bradycardic responses were significantly (P < 0.05) reduced by castration and by cyclosporine treatment (Table 2). Analysis of the baroreflex curves, relating decreases in HR responses to phenylephrine-induced increases in MAP, revealed a lesser steep regression line in the case of castrated or cyclosporine-treated rats; i.e., for a comparable rise in MAP there was a significantly (P < 0.05) smaller bradycardic response in these two groups compared with sham-operated rats (Fig. 1). The slope of the linear regression line, which represented BRS, was significantly (P < 0.05) and similarly reduced in castrated or cyclosporine-treated compared with sham-operated rats (−0.86 ± 0.06, −0.92 ± 0.06, and −1.47 ± 0.10 beats/min/mm Hg, respectively; Fig. 2A). On the other hand, treatment of castrated rats with cyclosporine caused no changes in the baroreflex curve (Fig. 1) or in BRS (Fig. 2A).

The subcutaneous injection of testosterone (1 mg/day for 6–8 days) to castrated rats increased the reflex bradycardic responses to phenylephrine (Table 2) and shifted the baroreflex curve toward that of the sham-operated rats (Fig. 1). The BRS (−1.45 ± 0.10 beats/min/mm Hg) of CAS + T rats was significantly (P < 0.05) higher than that of castrated rats and similar to that of sham-operated rats (Fig. 2A). In CAS + T rats, treatment with cyclosporine caused an upward shift in the baroreflex curve and significantly (P < 0.05) reduced BRS (Figs. 1 and 2A). The correlation coefficients of the regression lines were highly significant (P < 0.001) and ranged from 0.89 to 0.99.

To eliminate any role for the reduced pressor responsiveness to phenylephrine observed in cyclosporine-treated rats and its possible contribution to cyclosporine-induced impairment of reflex bradycardia, the HR responses to similar increases (approximately 35 mm Hg) in MAP were computed for individual rats, regardless of the dose of phenylephrine used, and the BRS was measured by calculation of the ratio ∆HR/∆MAP (El-Mas and Abdel-Rahman, 1993). The results showed that the reflex bradycardic (Fig. 3B) and BRS (Fig. 3C) responses, evoked by comparable increases in MAP (Fig. 3A), were significantly (P < 0.05) reduced by cyclosporine compared with the sham-operated rats. Similar reductions in the baroreflex bradycardia (Fig. 3B) and BRS (Fig. 3C) were demonstrated in CAS and CAS + CyA rats.

Changes in plasma testosterone levels evoked by castration, testosterone replacement, cyclosporine, or their combinations are shown in Fig. 2B. Plasma testosterone levels were significantly (P < 0.05) reduced by castration or cyclosporine compared with sham-operated levels (15.6 ± 5.3, 41.6 ± 9.9, and 105.4 ± 21.2 ng/dl, respectively). Treatment of CAS or CAS + CyA rats with testosterone restored the physiological levels of the hormone (Fig. 2B).

**Effects of Muscarinic or β-Adrenergic Blockade on Reflex Heart Rate Responses.** The effects of muscarinic or β-adrenergic blockade with atropine and propranolol, respectively, on peripherally mediated increases in MAP and reciprocal changes in HR are shown in Table 3 and Figs. 4 and 5.

In sham-operated rats, muscarinic blockade by atropine (1 mg/kg, i.v.) caused an upward shift of the baroreflex curve relating the pressor responses of phenylephrine to the associated reflex bradycardic responses and elicited a significant reduction in the BRS from −1.36 ± 0.14 to −0.59 ± 0.11 beats/min/mm Hg (Fig. 4A). Qualitatively similar effects for atropine were demonstrated in castrated and in cyclosporine-treated rats (Fig. 4, B and D). However, the percentage of reductions in BRS by atropine in castrated and cyclosporine-treated rats (30.34 ± 9.98 and 40.15 ± 7.99%, respectively) were significantly less than that of sham-operated rats (57.67 ± 4.37%; Table 3). The atropine-induced reductions in BRS of CAS + CyA rats were not statistically different from those of castrated or cyclosporine-treated rats (Table 3). The effects of atropine on the baroreflex curves and BRS were restored to sham-operated levels after testosterone replacement in CAS but not in CAS + CyA rats (Fig. 4, C and F; Table 3).

Contrary to the effect of atropine, β-adrenergic blockade by propranolol (1 mg/kg, i.v.) in sham-operated rats caused a slight upward shift in the baroreflex curve and insignificant decreases in the BRS from −1.59 ± 0.14 to −1.24 ± 0.21 beats/min/mm Hg (Fig. 5A). This represented a 22.35 ± 10.55% reduction in the BRS (Table 3), which suggests a minor contribution of the cardiac sympathetic activity in the reflex bradycardia. The effects of propranolol on the baroreflex curve of phenylephrine (Fig. 5) and the percentage re-

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**Table 1**

Baseline values of MAP (mm Hg) and HR (beats/min) in conscious, freely moving rats.

<table>
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<td>99.2 ± 3.1</td>
<td>452.5 ± 11.6*</td>
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* P < 0.05 compared with sham-operated value.
Introduction in BRS (Table 3) were not significantly altered by castration, cyclosporine, or their combination.

Discussion

Cyclosporine A, one of the most effective immunosuppressant agents, has been shown in clinical and experimental studies to impair the arterial baroreceptor function (Ryuzaki et al., 1997; Gerhardt et al., 1999; Lucini et al., 2000). The cyclosporine-induced baroreflex dysfunction in BRS (Table 3) were not significantly altered by castration, cyclosporine, or their combination.

Fig. 1. Baroreflex curves relating decrements in heart rate to increments in mean arterial pressure evoked by phenylephrine in conscious, freely moving, sham-operated, CAS rats and in CAS + T rats in the presence and absence of CyA. Values are the means of the pooled data obtained prior to atropine or propranolol administration. The standard errors of the means were omitted to reduce overcrowding of the figure.

Table 2

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<tr>
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<tr>
<td>CAS + CyA</td>
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</tr>
<tr>
<td>CAS + CyA + T</td>
<td>ΔMAP</td>
<td>5.4 ± 1.1</td>
<td>8.4 ± 1.7*</td>
<td>12.9 ± 1.8*</td>
<td>22.1 ± 2.5*</td>
<td>35.3 ± 3.1*</td>
</tr>
<tr>
<td>ΔHR</td>
<td>-6.9 ± 2.2</td>
<td>-10.8 ± 2.8*</td>
<td>-15.0 ± 2.9*</td>
<td>-20.9 ± 3.7*</td>
<td>-27.7 ± 3.3*</td>
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</table>

* P < 0.05 compared with sham-operated values.

Fig. 2. Effects of CyA on BRS (panel A) and plasma testosterone levels (panel B) in conscious, freely moving, sham-operated, CAS rats and in CAS + T rats. Values are expressed as mean ± S.E.M. of the pooled data obtained prior to atropine or propranolol administration. * and #, P < 0.05 compared with sham-operated and CAS + T rat values, respectively.
has been implicated in the pressor effect that develops during cyclosporine therapy (Gerhardt et al., 1999; Lucini et al., 2000). A similar correlation between hypertension and baroreflex impairment has been reported in humans (Goldstein, 1983) and experimental models of hypertension (Gordon and Mark, 1983; Abdel-Rahman and Wooles, 1987). The exact mechanism that underlies baroreflex impairment by cyclosporine is not clear. One possible explanation may involve the ability of cyclosporine to produce testicular dysfunction and lower plasma testosterone levels (Krueger et al., 1991; Bowman et al., 1997). Testosterone has been shown in a recent study from our laboratory to facilitate baroreflex responsiveness via enhancing cardiac vagal activity (El-Mas et al., 2001). The present study tested the hypothesis that cyclosporine impairs baroreflex function via reducing plasma levels of testosterone and inhibiting its facilitatory effect on cardiac vagal control. The effects of short-term cyclosporine administration on plasma testosterone levels and reflex bradycardic responses that developed secondary to baroreceptor loading by phenylephrine were evaluated in sham-operated rats as well as in castrated rats with and without testosterone replacement. Baroreflex curves relating increases in MAP evoked by phenylephrine to the associated decreases in HR were constructed, and the slopes were taken as a measure of BRS (El-Mas and Abdel-Rahman, 1992, 1998; El-Mas et al., 2001). The relative contributions of the sympathetic and parasympathetic components to the reflex bradycardic responses were also investigated.

The present findings that castration impairs arterial baroreceptor control of reflex bradycardia and that testosterone replacement restores BRS to sham-operated levels support our previous findings (El-Mas et al., 2001) and suggest that testosterone exerts a favorable effect on baroreceptor function. The current study presents evidence that implicates the male gonadal hormone testosterone in the depressant effect of cyclosporine on baroreflexes. This notion is supported by two observations. First, short-term castration or cyclosporine treatment caused remarkable reductions in plasma testosterone levels and similar attenuation of the baroreceptor control of reflex bradycardia, as suggested by the significant reduction in the slope of the regression line (BRS), relating peripherally mediated elevations in mean arterial pressure to the associated decreases in heart rate. Second, the ability of cyclosporine to impair reflex bradycardia was abolished when administered to testosterone-depleted (i.e., castrated) rats. Comparison of the slopes of the regression lines revealed that BRS values in castrated, cyclosporine-treated, and CAS + CyA rats were not statistically different. Taken together, the findings that cyclosporine lowered plasma testosterone levels and attenuated reflex bradycardia in sham-operated but not in castrated rats establish the first experimental evidence that inhibition of testosterone-mediated baroreflex facilitation may account, at

### Table 3

<table>
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<tr>
<th>Group</th>
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<th>Propranolol</th>
</tr>
</thead>
<tbody>
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<td></td>
<td>n</td>
<td>% Reduction</td>
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<tr>
<td>Sham</td>
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<tr>
<td>CAS</td>
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<tr>
<td>CAS + T</td>
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<td>CyA</td>
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<td>25.61 ± 13.32</td>
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* P < 0.05 compared with sham-operated values.
least partly, for the deleterious effect of cyclosporine on baroreflex function.

We have recently shown that the facilitatory effect of testosterone on baroreceptor control of reflex bradycardia is mediated via enhancement of cardiac vagal activity (El-Mas et al., 2001). The present study, therefore, attempted to investigate whether cyclosporine impairs baroreflexes through interfering with the modulatory effect of testosterone on vagal function. This objective was accomplished by evaluating the effect of selective muscarinic or β-adrenergic blockade by atropine and propranolol, respectively, on reflex bradycardic responses. Similar to earlier reports (Glick and Braunwald, 1965; Coleman, 1980), the present results obtained from sham-operated rats showed that the reflex bradycardic responses were mediated predominantly via increased cardiac vagal activity, because atropine caused approximately 60% reduction in BRS compared with only 20% in the case of propranolol. The effects of castration, cyclosporine, and their combination on the vagal contribution to reflex bradycardia paralleled their effects on BRS. The ability of atropine to reduce the predominantly vagally mediated reflex bradycardic responses was similarly attenuated in castrated rats and cyclosporine-treated rats. These findings suggest that testosterone depletion evoked surgically (by castration) or chemically (by cyclosporine) produced comparable impairment of the

Fig. 4. Effect of muscarinic blockade by atropine (1 mg/kg, i.v.) on baroreflex curves relating decreases in heart rate to phenylephrine-induced elevations in mean arterial pressure in conscious, freely moving, sham-operated, CAS and CAS + T rats in the presence and absence of CyA. Insets show the slopes (BRS, beats per minute per mm Hg) of the baroreflex curves. Values are expressed as mean ± S.E.M. *, P < 0.05 compared with the "before" values.
vagal component. The view that the inhibitory effect of cyclosporine on vagal activity is testosterone-related gains further support from the observation that treatment of castrated rats with cyclosporine caused no additional decline in the overall contribution of the vagal component to reflex bradycardia. In effect, the reduction in BRS evoked by atropine in CAS/H11001/CyA rats was not statistically different from that of castrated rats. Collectively, these findings may plausibly suggest that cyclosporine counteracts testosterone-mediated baroreflex enhancement via compromising its facilitatory effect on the cardiac vagal control.

It is important, however, before this conclusion is accepted, to comment on two potential limitations. The first relates to the possibility that the lack of an action of cyclosporine on BRS in castrated rats may be accounted for by the presence of a significantly lower baseline BRS in these rats as compared with sham-operated rats. It could be argued, therefore, that the BRS in castrated rats may have reached its nadir so that cyclosporine cannot depress it further. However, this issue may be addressed by the present finding that muscarinic blockade by atropine produced a significant attenuation of the BRS in castrated rats. The susceptibility of the remaining baroreceptor activity in castrated rats to additional attenuation by atropine rules out the possibility that its low levels can account

**Fig. 5.** Effect of β-adrenergic blockade by propranolol (1 mg/kg, i.v.) on baroreflex curves relating decreases in heart rate to phenylephrine-induced elevations in mean arterial pressure in conscious, freely moving, sham-operated, CAS and CAS + T rats in the presence and absence of CyA. Insets show the slopes (BRS, beats per minute per mm Hg) of the baroreflex curves. Values are expressed as mean ± S.E.M.
for the absence of cyclosporine effect on BRS in these rats. The second limitation pertains to the finding that cyclosporine significantly reduced BRS in testosterone-replaced castrated rats, which have restored physiological levels of the hormone. This finding should not be interpreted to argue against a modulatory role for testosterone in cyclosporine-baroreflex interaction. Instead, it may suggest that the inhibitory effects of cyclosporine on the baroreflex and vagal responses to testosterone are not due to inhibition of the testicular release of the hormone per se but due to the interaction of cyclosporine with specific receptors or sites within the baroreflex arc that mediate the hormone effect on baroreflex function. Possible targets for such interaction are the nucleus ambiguus and the dorsal motor nucleus of the vagus, brainstem areas in which androgen receptors have been identified (Sheridan and Weakler, 1982; Freeman, 1988) and are known to play a crucial role in the control of central vagal discharges (Ciriello and Calaresu, 1979; Van Giersbergen et al., 1992). More studies are needed, however, to determine the exact mechanism(s) involved in the interaction between cyclosporine and gonadal hormones on baroreflex function.

The present finding that cyclosporine reduced the pressor responsiveness to phenylephrine deserves a comment. Androgens and gonadal hormones on baroreflex function. Possible targets for such interaction are the nucleus ambiguus and the dorsal motor nucleus of the vagus, brainstem areas in which androgen receptors have been identified (Sheridan and Weakler, 1982; Freeman, 1988) and are known to play a crucial role in the control of central vagal discharges (Ciriello and Calaresu, 1979; Van Giersbergen et al., 1992). More studies are needed, however, to determine the exact mechanism(s) involved in the interaction between cyclosporine and gonadal hormones on baroreflex function.

Acknowledgments

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References


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