Sympathetic Nervous System and Deoxycorticosterone-Saline Hypertension

We wish to comment on the article by de Champlain and Ameringen (Circ Res 31:617–628, 1972) in which they imply the involvement of the peripheral sympathetic nervous system in the etiology of deoxycorticosterone (DOCA)-saline hypertension. In the discussion of their article, the work of Clarke et al. (Life Sci [I] 9:1097–1108, 1970) has been misquoted. Contrary to the authors’ impression, we did not investigate the effect of adrenal medullectomy on the production of this type of hypertension; in fact, we drew no conclusions as to the role of the adrenal glands. Consequently, their passage concerning the possible occurrence of adrenal-regeneration hypertension as a complicating influence in our study is without foundation.

Like de Champlain and Ameringen, we also used 6-hydroxydopamine (6-OH-DA) to inhibit peripheral sympathetic neuronal function; but, unlike them, we obtained no qualitative or quantitative change in the time course of the hypertension. They explained this discrepancy on the grounds that our biweekly dosage schedule of 6-OH-DA (compared with their weekly treatment) was probably too infrequent to maintain a state of efficient sympathectomy. Contrary to this assumption, we have shown that this treatment schedule does completely prevent hypertension resulting from chronic exposure to environmental stress (Smookler et al., Pharmacologist, 1971, and Smookler et al., Fed Proc, in press).

Furthermore, it is important to note that their hypertensive model differed from ours. de Champlain and Ameringen used unilaterally adrenalectomized rats which were given DOCA only once a week. These differences appear to have resulted in a far less fulminating hypertension than that obtained in our rats with intact adrenals which were given DOCA daily. Thus, at the present time, the evidence for sympathetic neuronal involvement in DOCA-saline hypertension remains debatable.

However, the answer to this question may be close to final resolution in view of the evidence advanced by de Champlain and Ameringen concerning the marked dependence of systemic blood pressure on adrenal catecholamine secretion following 6-OH-DA treatment. It would be highly desirable therefore to reinvestigate this form of hypertension utilizing chemical sympathectomy in conjunction with bilateral adrenal demedullation. This latter surgical technique can be accomplished with much less adrenal cortical damage than is instituted normally for the production of adrenal-regeneration hypertension. Furthermore, adrenal-regeneration hypertension, should it occur, would be reflected in the appropriate control group. Finally, it should not be overlooked that DOCA-saline and adrenal-regeneration hypertension are closely allied, since both originate from the production of excessively high plasma mineralocorticoid levels.

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REPLY TO THE ABOVE LETTER

We would like to apologize to D. E. Clarke, H. H. Smookler, and H. Barry for having misquoted one of their papers in the Discussion of our recent paper (Circ Res 31:617–628, 1972). On page 625 we wrote, "Moreover, the fact that adrenal medullectomy in combination with 6-OH-DA treatment did not prevent the development of hypertension," referring wrongly to the work of Clarke et al. (Life Sci [I] 9:1097–1108, 1970). That statement was meant rather to refer to the work of Finch and Leach (Eur J Pharmacol 11:388–391, 1970) which was inadvertently omitted from our bibliography during the final retyping of our manuscript.

In their letter Clarke et al. made additional comments which we would like to answer. They pointed out that our hypertensive model differed from their own in that our rats were unilaterally adrenalectomized and given DOCA only once a week. First of all, we removed only one adrenal gland for the group of rats in which we studied the effect of acute adrenalectomy under anesthesia. In the group in which we studied the development of hypertension, both adrenal glands were present and only the left kidney was removed, as stated in Methods, fifth paragraph. Moreover, the pattern of development of hypertension in our study was as fulminating as it was in the study of Clarke et al. Six weeks after beginning the DOCA and sodium treatment, the average systolic blood pressure recorded with the same technique as that used by Clarke et al. in unanesthetized rats was 207 mm Hg (Table 1 of our paper); however, Clarke et al. reported an average of 195 mm Hg after 4½ weeks of treatment. In some of our figures the average blood pressure was lower, but this pressure represented the mean blood pressure recorded under anesthesia through the carotid artery. Either schedule of injection of DOCA (5 mg/kg in oil daily or 10 mg suspension weekly) in our experiment did not affect the pattern of development of hypertension. We did in fact find the same abnormalities in catecholamine metabolism in rats using both schedule of injections.

Although the model of hypertension used by Clarke et al. was quite similar to ours, there were nevertheless major differences in the results obtained after treatment with 6-OH-DA. In their study, the treatment with 6-OH-DA did not prevent the development of hypertension after the administration of DOCA and sodium for 4½ weeks; however, in our study the treatment with 6-OH-DA prevented the development of hypertension after the administration of DOCA and sodium for 5 weeks. The discrepancy between our findings and those of Clarke et al. might be explained on the basis of the schedule of administration of 6-OH-DA. In our study,
rats were treated from birth with 6-OH-DA (100 mg/kg) administered at weekly intervals. When they reached a body weight of 100 g the treatment with DOCA and sodium was started and the weekly administration of 6-OH-DA was continued. In the study of Clarke et al., the treatment with 6-OH-DA was started 1 week before DOCA administration and a dose of 100 mg/kg was repeated at 2-week intervals. We indicated in our Discussion that 2-week intervals between injections of 6-OH-DA were too long to maintain efficient sympathectomy based on our own observation that an important number of fibers started to regrow 1 week after treatment with 6-OH-DA (de Champlain, Can J Physiol Pharmacol 49:345-355, 1971). Also, a normal response to tyramine was restored, and the supersensitivity to norepinephrine had almost disappeared 2 weeks after the administration of 6-OH-DA (Nadeau et al., Can J Physiol Pharmacol 49:36-44, 1971). These findings and the fact that blood pressure and heart rate had returned to normal within 2 weeks after injection of 6-OH-DA suggest that the major part of sympathetic function was restored in these rats at a time when the number of fibers and the content of endogenous norepinephrine were only partially restored. In support of this interpretation, Smookler and Clarke recently provided direct evidence that the sympathetic nerve function in the rat is restored by 70% 14-15 days after injection of 6-OH-DA, (Proc 5th Int Congr Pharmacol, p 218, 1972).

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