To the Editor:

I read with interest the paper “Centrally Mediated Effects of Bromocriptine on Cardiac Sympathovagal Balance” published in Hypertension, July 2001.1 The authors cite a report by Przuntek et al2 published in 1992 that suggested that bromocriptine treatment lessened mortality in patients with Parkinson disease. The authors presumed that this putative cardioprotective effect can be related to withdrawal of cardiac sympathetic activity leading to fewer life-threatening ventricular arrhythmias. Unfortunately, the authors failed to mention that since 1992, long-term studies in Australia3 and France4 have failed to replicate the findings cited in the Przuntek paper. The Australian and French studies were of 10-year durations and found no evidence of a cardioprotective effect from bromocriptine.

Over the past 25 years, bromocriptine has been studied in the treatment of clinical indications such as acromegaly, hyperprolactinemia, postpartum lactation suppression, cocaine craving, and diabetes mellitus, in addition to Parkinson disease. Rather than a cardioprotective effect, bromocriptine shares with other ergot alkaloids the property of vasoconstriction, with the potential for serious tissue injury. Hypertension5 and cardiac injury6 have been reported in association with bromocriptine use in lactation suppression. Seizures and myocardial infarction were reported in association with bromocriptine use in the treatment of cocaine craving, which led the Italian Health Ministry to request the withdrawal of bromocriptine for use in cocaine craving.7 Finally, in clinical trials of bromocriptine for the treatment of Type 2 diabetes presented to the Food and Drug Administration, a relative risk of myocardial infarction of 2.9 after bromocriptine treatment was found.8

In the design of the study by Franchi and colleagues, the investigators used single oral doses of bromocriptine with measurements at baseline and 180 minutes after bromocriptine administration. It has long been known that bromocriptine has active metabolites9 that persist in the body for up to 120 hours. Hydroxylated metabolites of bromocriptine have been found to be effective in reducing prolactin in rats.10 Dr. Franchi and colleagues did not investigate pharmacologically active bromocriptine metabolites.

Finally, medical journals have recognized the need for objectivity in the publication of clinical research findings.11 In the July 2001 edition of Hypertension, 21 articles were published under the heading “Scientific Contributions.” Of these 21 articles, this paper is one of two that failed to include an acknowledgments section. One can assume that no financial, institutional, or manuscript preparation assistance was provided in support of the publication of this research. Perhaps all published papers should include an acknowledgments section with the appropriate response to allow the reader to assess the potential for conflicts of interest.

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Response

In reply to the letter by Dr D.J. Petro referring to our article “Centrally-mediated effects of bromocriptine on cardiac sympathovagal balance” published in Hypertension, July 2001,1 I would like to point up the following issues:

1. The design and the results of the study were chiefly aimed at evaluating the effects (peripherally and centrally, as well) of acute bromocriptine administration on the cardiac sympathovagal balance. The influence of long-active metabolites of the drug lies outside our specific purpose. Moreover, the references cited by Dr Petro (Reavill et al, 1980,2 Valente et al, 1997?) referred only to data obtained in experimental animals.
2. The potential role for serious tissue injuries caused by the vasoconstrictive effects of bromocriptine (Watson et al, 1992;4 Ellenhorn MJ, 1997;5 Food and Drug Administration, 1998) referred to pathological conditions inadequate to properly evaluate a baseline pharmacological action. For example, Watson et al4 assessed the risk of postpartum hypertension in a peculiar subset of patients, i.e., those with antepartum pregnancy-induced hypertension. It is conceivable that observations made in “high-risk” subgroups cannot be extended to the general population or at least should be confined to that particular population.
3. Regarding the cited report by Przuntek et al,3 the results of our investigation disagree with those arrived at by these authors. In the discussion section of our article, we observed that “The increase in the cardiac sympathetic tone (as indicated by higher values of the LF component), observed after acute oral bromocriptine, seems to be in disagreement with the finding of the reduction in cardiac sympathetic activity in L-Dopa–treated patients with Parkinson’s disease given bromocriptine, as reported by Przuntek et al.” This discrepancy can probably be related to the fact that (unlike Przuntek et al) we evaluated the drug effects after an acute and not a chronic administration and with healthy subjects rather than in disease conditions.” In the same section, we also observed that, with subjects in the supine position, “The administration of bromocriptine alone was associated with a reduction in blood pressure and an increase in cardiac sympathetic drive (as induced by higher values of LF), which is probably related to the sympathetic effenter loop of the baroreflex. Nevertheless plasma norepinephrine levels were reduced . . . These findings seem controversial, but they are likely explained by the combined effects of opposite actions exerted by bromocriptine in vivo. In fact, bromocriptine is able to lower norepinephrine levels, thus causing hypotension; on the other hand, reduced blood pressure values induced a reflex activation of the sympathetic output (as indicated by the increased LF component in the supine position).” Thus, no presumption of any putative cardioprotective effect has
Letters to the Editor

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Response

We are responding to several points made by Dr Majima in regard to our recent article in Hypertension.¹

(1) Dr Majima wanted us to provide an explanation for the ~7 mm Hg drop in mean blood pressure (MBP) from the pretreatment period to Week 1 (Figure 1 in our article). This request was surprising, because (a) the difference was not statistically significant, (b) it’s usual to observe such a variation in BP within a few days after surgically installing the telemetry device, as previously reported,² and (c) by the end of Week 1 and 2 we were expecting instead a 40- to 50-mm Hg increase in BP as reported by Dr Majima’s group.³

As we stated in our article, MBP was 115±3 mm Hg in normal Brown Norway rats compared with 118±3 mm Hg in Brown Norway Katholiek (BNK) rats. Hence, there is also no difference between the 2 strains in terms of BP, similar to Dr Majima’s data.³

Our BP values were about 12 to 14 mm Hg higher than Dr Majima’s, but that’s normal because we measured BP in the United States with our equipment, whereas Dr Majima’s were done in Japan with their equipment.

(2) As we indicated in the article, Dr Majima visited our laboratory in an attempt to reconcile the different findings between our study and his, but we were not able to do so. We included him in the acknowledgments as a way of expressing our gratitude for his generous assistance. Thus, there is no letter to this effect, as we merely wished to acknowledge his courtesy to us. It does not seem logical to me that it would be necessary for us to first write to Dr Majima and ask for his permission to thank him for helping us.

Moreover, the Editorial Board of Hypertension never asked us to provide them with any documentation regarding this matter.

In our article we stated “(1) normal BN rats were given a subcutaneous infusion of Ang II or high salt diet alone or combined with icatibant . . . and (2) BNK rats were given a subcutaneous infusion of a nonpressor dose of Ang II or high salt diet . . . we were unable to reproduce any of their findings or those of Madeddu et al.” There was a mistake, and we should have stated “(1) normal BN rats were given high salt diet alone or combined with icatibant . . . and (2) BNK rats were given a subcutaneous infusion of a nonpressor dose of Ang II or high salt diet . . . we were unable to reproduce any of their findings or those of Madeddu et al.” Dr Majima did not participate with us in the protocol dealing with the effect of icatibant infusion on the pressor effect of Ang II in normal BN rats. Dr Majima stated that the original results were confirmed while participating with us on a protocol involving BNK rats infused with vehicle or subpressor dose of Ang II. That is wrong, because when we administered a subpressor dose of Ang II or high salt diet . . . we were unable to reproduce any of their findings or those of Madeddu et al.”

Dr Majima did not participate with us in the protocol dealing with the effect of icatibant infusion on the pressor effect of Ang II in normal BN rats. Dr Majima also commented that the original results were confirmed while participating with us on a protocol involving BNK rats infused with vehicle or subpressor dose of Ang II. That is wrong, because when we administered a subpressor dose of Ang II, systolic blood pressure was slightly higher in BNK rats compared with rats given vehicle; however, direct arterial MBP in awake and restrained rats was similar in both groups. For that reason, we opted for telemetry and explained the rationale for its use in our paper.

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Questioning the Cardioprotective Effect of Bromocriptine Treatment
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