Reply to Letter to the editor

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Received 25 June 1999; accepted 25 June 1999

To the Editor:

We thank Dr. Pagliaro for his comments. In his letter Dr. Pagliaro focused on two points of the discussion of chronotropic effects of endogenous nitric oxide (NO) in our review [1]; (1) the use of N\textsuperscript{\textdagger}nitro-L-arginine-methyl ester (l-NAME) and (2) a possible involvement of autonomic reflexes due to increases in blood pressure.

l-NAME is a widely used prodrug to inhibit NO-synthase (NOS) because of its convenient water solubility. To effectively inhibit NOS, l-NAME has to be deesterified to N\textsuperscript{\textdagger}nitro-L-arginine, and in whole blood its half-life is 29 min [2]. Thus, it is unlikely that the intact ester has any considerable effect in-vivo. It is known that high concentrations of l-NAME can block muscarinic receptors in-vitro [3]. In-vivo this blockade would result in an atropine like tachycardia, but there is no evidence of an antimuscarinergic effect of orally applied l-NAME.

The baroreceptor reflex balances sudden but not sustained changes in blood pressure. In hypertension there is a resetting of baroreceptors resulting in diminished baroreceptor induced pulse frequency (relatively diminished parasympathetic nerve activity) at any given blood pressure [4]. This was also observed in a chronically hypertensive transgenic mouse strain [5]. Thus, the bradycardia observed in normal mice treated for 3 weeks with l-NAME and in mice lacking the eNOS gene is most likely not a consequence of the concommitant mild increase in blood pressure. This interpretation is consistent with our observation that treatment of mice lacking the eNOS gene with l-NAME resulted in further bradycardia in the absence of any change of blood pressure [6]. It is also consistent with a recently published study demonstrating that isolated atria of mice lacking the eNOS gene have a normal response to muscarinergic stimulation [7].

Finally, measurements of blood pressure and heart rate were obtained from conscious and trained animals [6,8] excluding any unspecific effect of anaesthesia. This was not the case in the studies cited by Dr. Pagliaro. Therefore, we believe that the references cited in our review are appropriate and that these investigations have considerable methodological advantages to demonstrate a negative chronotropic effect of endogenous NO.

References


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