Blood Pressure in Mutant Rats Lacking the 5-Hydroxytryptamine Transporter

To the Editor:

Although 5-HT uptake inhibitors are widely used as antidepressants, the role of 5-HT in the control of systemic blood pressure is far from clear.1 In a recent issue of Hypertension, Ni et al reported that 5-hydroxytryptamine (5-HT) transporter (SERT) expression was increased, whereas SERT function was decreased in aorta of rats with DOCA salt and N\textsuperscript{-}nitro-L-arginine (L-NNA)-induced hypertension.2 We have observed that several 5-HT receptors are induced in leukocytes of hypertensive patients.3 These 2 observations could point at a functional response of the serotonin system to counter prohypertensive forces. We used the recently generated and unique SERT knockout rat to investigate whether the constitutive absence of SERT affected blood pressure and aggravated the development of hypertension and renal damage on NO synthesis inhibition.

A target-selected \textit{N} \textit{ethyl}-\textit{N} \textit{nitroso}urea–driven mutagenesis approach was used in Wistar rats to inactivate genes.4 High-throughput resequencing of genes of interest in a library of mutant rats resulted in the identification of a premature stop codon in the serotonin transporter. We have established that the homozygous SERT knockout (SERT\textsuperscript{\textminus/\textminus}) rat completely lacks functional SERT in the brain (data not shown). Furthermore, 5-HT in blood platelets, which plays a crucial role in vasoconstriction and has mitogenic activity in vascular smooth muscle, was almost completely lacking in SERT\textsuperscript{\textminus/\textminus} rats (Figure).

To characterize the SERT\textsuperscript{\textminus/\textminus} rat with respect to the cardiovascular system, we measured systolic blood pressure (SBP) in female SERT\textsuperscript{\textminus/\textminus}, SERT\textsuperscript{\textplus/\textminus}, and SERT\textsuperscript{\textplus/\textplus} rats under control conditions and during chronic L-NNA administration (500 mg/L of drinking water). Under control conditions, there were no differences in SBP between genotypes. Left ventricular (LV) weight/body weight and increases in SBP and LV/body weight during L-NNA (both P<0.01; 2-way ANOVA) were similar in all 3 of the groups (Table). Furthermore, under control conditions or L-NNA treatment, no differences were found in proteinuria, plasma urea and creatinine, and renal morphology (data not shown).

SERT-deficient mice also display normal blood pressure, although LV weight is reduced.5 It is at this functional level that the present data complement the data presented by Ni et al.2 From our analysis in the SERT\textsuperscript{\textminus/\textminus} rat, it seems that the integrative role for SERT on blood pressure control by systemic hemodynamics and by the kidney to protect against the hypertensive effects of NO-shortage is limited. Furthermore, a protective role against glomerular damage caused by NO deficiency could not be substantiated.

Disclosures

None.

| SBP (mm Hg) and LV/Body Weight (mg/g) Measured Under Control Conditions and During 3 Weeks of L-NNA Treatment in Female SERT\textsuperscript{-/\textminus}, SERT\textsuperscript{+/-}, and SERT\textsuperscript{++/\textplus} Rats |
|---|---|---|---|---|---|
| Groups | N | Baseline | Week 1 | Week 2 | Week 3 |
| Control conditions |
| SERT\textsuperscript{+/-} | 5 | 115±6 | 110±2 | 108±3 | n.m. |
| SERT\textsuperscript{+/-} | 4 | 117±6 | 109±4 | 117±4 | n.m. |
| SERT\textsuperscript{++/\textplus} | 5 | 109±3 | 125±5 | 114±3 | n.m. |
| N\textsuperscript{(o)-nitro-L-arginine} |
| SERT\textsuperscript{+/-} | 4 | 109±4 | 133±5 | 153±5 | 157±9 |
| SERT\textsuperscript{+/-} | 4 | 127±9 | 152±4 | 174±1 | 178±13 |
| SERT\textsuperscript{++/\textplus} | 4 | 114±5 | 137±12 | 157±11 | 166±2 |

Mean±SEM, n.m. indicates not measured.

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