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Acute antihypertensive action of Tempol in the spontaneously hypertensive rat

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Chen X, Patel K, Connors SG, Mendonca M, Welch WJ, Wilcox CS. Acute antihypertensive action of Tempol in the spontaneously hypertensive rat. Am J Physiol Heart Circ Physiol 293: H3246–H3253, 2007. First published October 12, 2007; doi:10.1152/ajpheart.00957.2007.—Acute intravenous Tempol reduces mean arterial pressure (MAP) and heart rate (HR) in spontaneously hypertensive rats. We investigated the hypothesis that the antihypertensive action depends on generation of hydrogen peroxide, activation of heme oxygenase, glutathione peroxidase or potassium conductances, nitric oxide synthase, and/or the peripheral or central sympathetic nervous systems (SNSs). Tempol caused dose-dependent reductions in MAP and HR (at 174 μmol/kg: ΔMAP, −57 ± 3 mmHg; and ΔHR, −50 ± 4 beats/min). The antihypertensive response was unaffected by the infusion of a pegylated catalase or by the inhibition of catalase with 3-amino triazole, inhibition of glutathione peroxidase with buthionine sulfoximine, inhibition of heme oxygenase with tin mesoporphyrin, or inhibition of large-conductance Ca2+–activated potassium channels with iberiotoxin. However, the antihypertensive response was significantly (P < 0.01) blunted by 48% by the activation of adenosine 5′-triphosphate-sensitive potassium (KATP) channels on smooth muscle cells with cromakalim during maintenance of blood pressure with norepinephrine and by 31% by the blockade of these channels with glibenclamide, by 40% by the blockade of nitric oxide synthase with Nω-nitro-L-arginine methyl ester (L-NAME), and by 40% by the blockade of ganglionic autonomic neurotransmission with hexamethonium. L-NAME and hexamethonium were additive, but glibenclamide and hexamethonium were less than additive. The central administration of Tempol was ineffective. The acute antihypertensive action of Tempol depends on the independent effects of potentiation of nitric oxide and inhibition of the peripheral SNS that involves the activation of KATP channels.

superoxide dismutase; nitric oxide synthase; sympathetic nervous system; catalase; adenosine 5′-triphosphate-activated potassium channels

OXIDATIVE STRESS UNDERLIES hypertension in many animal models (46). Superoxide (O2•−) can raise blood pressure (BP) by central (53) or peripheral mechanisms (32). Nitric oxide (NO) can reduce BP by vascular and central actions to reduce the sympathetic nervous system (SNS) (51). NO is biodegraded by O2•−, which is itself metabolized by superoxide dismutase (SOD) to the more stable H2O2 that can have vasoconstrictor or vasodilator actions on blood vessels (25), mediate or release an endothelium-derived hyperpolarizing factor (31), and activate large-conductance calcium-activated potassium channels (BKs) (42) and adenosine 5′-triphosphate (ATP)-sensitive potassium (KATP) channels on vascular smooth muscle cells (VSMCs) (9, 24).

4-Hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl (Tempol) is a stable ampholyte, membrane-permeable piperidine nitroxide that has SOD (23) and catalase mimetic activity (22). The acute intravenous injection of nitroxides into spontaneously hypertensive rats (SHRs) reduces the mean arterial pressure (MAP) and heart rate (HR) (35) in proportion to the in vitro SOD mimetic activity (35). The SHR is a model of increased oxidative stress that exhibits a more sensitive BP-lowering response to acute intravenous injection of Tempol than does the Wistar-Kyoto rat (39). Xu et al. (48, 49) and Shokoji et al. (40) have reported that the acute antihypertensive response to Tempol in rat models is mediated by inhibition of the peripheral SNS, whereas Campese et al. (4) have reported that the central administration of Tempol can reduce BP in the rat. Tempol also activates BKs on VSMCs (50). An interaction with heme oxygenase (HO), which generates the antioxidants bilirubin and biliverdin and the vasodilator compound carbon monoxide (CO), could contribute to a reduction in BP (37). Another potential target is the KATP channels that modulate vascular tone (38) and the activity of which is regulated by a redox-sensitive thiol in the active site (6, 13).

We tested the hypothesis that the acute antihypertensive actions of Tempol in the anesthetized SHR depend on catalase mimetic activity, the activation of BK or KATP channels, HO, NO synthase (NOS), or the central or peripheral SNSs.

METHODS

Animal Methods

Procedures were approved by the Georgetown University Animal Care and Use Committee and followed closely a prior protocol (35). Briefly, male SHRs were anesthetized with halothane, maintained with thiobutabarbital (Inactin, 100 mg/kg ip; Sigma, St. Louis, MO), and placed on a thermostatically controlled table where a tracheotomy was performed, the left jugular vein was cannulated for infusion, and the femoral artery was cannulated for digital recording of MAP and HR (Micro-Med, Louisville, KY). Rats received 0.154 M NaCl at 2 ml/h to maintain euvolement (35, 39).

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Either full dose-response relationships for Tempol (17, 54, 72, 131, 174, and 270 μM/kg iv) or the response to a single fully effective dose of 174 μM/kg iv was compared after pretreatment with a vehicle and, after a 30- or 45-min period, after a blocking drug (35). The peak changes in MAP and HR from baseline were recorded. We did not detect any time-related differences between groups. Control studies (n = 7) established a similar fall in MAP [ΔMAP, −64 ± 6 and −59 ± 6 mmHg, not significant (NS)] and in HR (∆HR, −46 ± 6 and −42 ± 4 beats/min, NS) with the first and second 174 μM/kg iv doses of Tempol given during vehicle infusion. Thirty minutes were allowed between the two injections of Tempol for recovery of BP and HR. Where the blocking drug reduced the baseline BP, an infusion of norepinephrine was given to restore BP to control values (39).

Study Protocols

The aim of series 1 was to assess the role of the catalase mimetic action of Tempol. SHRs (n = 5) were given 174 μM/kg Tempol, followed by an infusion with the catalase inhibitor 3-amino-1,2,4-triazole (3-AT, 6.4 μM/kg iv), during which the test dose of Tempol was repeated. This dose of 3-AT blocks catalase effectively in vivo (19). Other SHRs (n = 6) received graded doses of Tempol during vehicle infusion followed, after 45 min, by polyethylene glycol (PEG)-catalase (2,000 units iv bolus), during which the Tempol dose-response study was repeated. This dose of PEG-catalase is effective in vivo (41). This was assessed further after glutathione depleting. Groups of SHRs (n = 5) were tested with 174 μM/kg Tempol after 2 wk of administration of a vehicle or the glutathione-depleting agent buthionine sulfoximine (BSO; 30 mmol/l) added to the drinking water. This dose of BSO reduces glutathione levels threefold and causes oxidative stress (44). An additional group was given 3-AT as in series 1 after pretreatment with a vehicle or BSO for 2 wk.

The aim of series 2 was to assess the role of HO. Alternate SHRs were administered a vehicle (n = 7) or tin mesoporphyrin (SnMP; 40 μM/kg iv bolus injection; n = 8). After 20 min, a dose-response study for Tempol was undertaken. This dose of SnMP blocks 84% of HO activity and reduces CO generation in renal microdialysate by 50% (37).

The aim of series 3 was to assess the role of potassium channels. SHRs were given a test dose of 174 μM/kg Tempol. Thereafter, they were infused with either the BK channel blocker ibetirocin (IBTX; 0.1 or 0.3 mg/kg iv for 5 min; n = 6) or the KATP channel blocker glibenclamide (15 mg/kg iv for 5 min; n = 6), followed, after 30 min, by a repeated dose of 174 μM/kg Tempol. This dose of IBTX (0.1 mg/kg) blunts 55% of the fall in MAP produced by nitroglycerin in vivo (1), whereas this dose of glibenclamide blocks vascular KATP channels in vivo (5). To determine the role of KATP channels further, SHRs were infused with a vehicle (n = 7) or the KATP channel-activating drug cromakalim (50 μg iv and 50 μg·kg⁻¹·min⁻¹; n = 8). Cromakalim produced a dramatic fall in BP (153 ± 5 vs. 68 ± 6 mmHg). Therefore, norepinephrine (1–3 μg·kg⁻¹·min⁻¹ iv) was infused during cromakalim to restore the BP toward control values. This dose of cromakalim opens KATP channels on VSMCs in vivo (36).

The aim of series 4 was to assess the individual effects of NOS, KATP channels, and the SNS and the interactive effects of the SNS and NOS or KATP channels on the response to Tempol. To assess the role of NOS, SHRs (n = 12) were given a test dose of 174 μM/kg Tempol. Thereafter, they were infused with Nω-nitro-L-arginine methyl ester (L-NAME) for 45 min, and the Tempol dose was repeated. To assess the role of the SNS, SHRs (n = 10) received the ganglion-blocking drug hexamethonium (10 mg/kg iv). Since this led to a profound reduction in BP (163 ± 3 vs. 106 ± 5 mmHg) and HR (365 ± 9 vs. 315 ± 8 beats/min), norepinephrine (1–2 μg·kg⁻¹·min⁻¹ iv) was infused with hexamethonium to restore MAP toward basal levels (as in series 4). After 15 min of norepinephrine, rats were tested with 174 μM/kg of Tempol. To assess whether the effects of blockade of NOS and SNS are independent, a second group of SHRs (n = 7) received an infusion of L-NAME and an injection of hexamethonium. This led to a modest reduction in MAP (164 ± 5 vs. 133 ± 11 mmHg) and HR (404 ± 14 vs. 338 ± 15 beats/min), but norepinephrine was not given since it provokes cardiac arrhythmias. To assess whether effects of the blockade of SNS and KATP channels are independent, a third group of SHRs (n = 8) received hexamethonium and norepinephrine (as described above) with glibenclamide (15 mg/kg iv) over 5 min, followed by a test dose of 174 μM/kg of Tempol. The interactive effect of glibenclamide and L-NAME could not be assessed, since this combination caused cardiac arrest in the first three rats tested, perhaps due to coronary ischemia (38).

The aim of series 5 was to assess the central effects of Tempol. SHRs (n = 6) were placed in a stereotactic device (10). The lateral cerebral ventricle was cannulated (10), a steel cannula was glued in place, and after 45 min graded doses of Tempol (0.2, 0.5, 0.7, 1.3, 1.7, 2.7, and 5.1 μM/kg) were administered intracerebroventricularly every 15 min in 2-μl volumes of vehicle (10). As a positive control, 50 ng of ANG II were administered intracerebroventricularly at the completion.

Drugs. 3-AT, BSO, glibenclamide, hexamethonium, IBTX, L-NAME, norepinephrine, PEG-catalase, PEG-SOD, Tempol, and thioctabartar (Inactin) were purchased from Sigma. Halothane was purchased from Halocarbon Laboratories (River Edge, NJ), and tin mesoporphyrin was purchased from Frontier Scientific (Logan, UT). Glibenclamide was initially dissolved with 0.1 N NaOH and then slowly diluted with dextrose in water (50 g glucose/l distilled water) during sonication (5). Other drugs were dissolved in 0.154 M NaCl solution.

Statistics

The data are presented as means ± SE. Data were analyzed by one-way ANOVA with Bonferroni’s post hoc test, where appropriate. Where differences in the pretest levels of MAP were apparent, fractional changes in MAP and HR were compared, as recommended (16). A P value of <0.05 was considered statistically significant.

Table 1. Basal data for body weight, MAP, and HR

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<tr>
<th>Series/Group</th>
<th>n</th>
<th>Body Weight, g</th>
<th>MAP, mmHg</th>
<th>HR, Beats/min</th>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Vehicle</td>
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<td>291 ± 7</td>
<td>178 ± 6</td>
<td>382 ± 9</td>
</tr>
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<td>265 ± 7</td>
<td>155 ± 5</td>
<td>368 ± 4</td>
</tr>
</tbody>
</table>

Values are means ± SE before administration of drugs; n, number of rats; MAP, mean arterial pressure; HR, heart rate; 3-AT, 3-aminoatrazole; BSO, buthionine sulfoximine; SnMP, tin mesoporphyrin; IBTX, iberiotoxin; Glib, glibenclamide; CRK, cromakalim; L-NAME, Nω-nitro-L-arginine methyl ester; Hex, hexamethonium; PEG, polyethylene glycol; iv, intracerebroventricular. P value (ANOVA) is not significant for all groups.
RESULTS

The body weight, MAP, and HR before drug administration did not differ between groups (Table 1). Tempol caused a rapid reduction in MAP and HR that had returned toward baseline over 16 min (Fig. 1).

Series 1. MAP and HR were similar in rats pretreated with vehicle or PEG-catalase (178 ± 6 vs. 186 ± 8 mmHg and 382 ± 9 vs. 381 ± 7 beats/min, NS). Neither pretreatment with PEG-catalase (Fig. 2) nor with 3-AT (data not shown) altered the dose-dependent reduction in MAP or HR with Tempol. MAP and HR were similar in rats pretreated for 2 wk with vehicle or BSO (176 ± 3 vs. 176 ± 6 mmHg and 382 ± 13 vs. 387 ± 8 beats/min, NS) and in those given 3-AT after BSO (169 ± 4 mmHg and 372 ± 6 beats/min, NS vs. vehicle). The fall in BP and HR with Tempol after the vehicle (ΔMAP, 50 ± 4 mmHg; and ΔHR, 50 ± 3 beats/min) was not different after BSO alone (ΔMAP after BSO −51 ± 3 mmHg and ΔHR −52 ± 6 beats/min; NS) or after BSO and 3-AT (ΔMAP, −48 ± 3 mmHg; and ΔHR, −49 ± 10 beats/min; n = 5, NS vs. vehicle).

Series 2. MAP and HR were similar in rats pretreated with vehicle or SnMP (178 ± 6 vs. 172 ± 6 mmHg and 382 ± 9 vs. 390 ± 8 beats/min, NS). Inhibition of HO with SnMP did not modify the dose-dependent effects of Tempol (Fig. 3).

Series 3. MAP and HR were similar in rats receiving a vehicle or IBTX (162 ± 3 vs. 161 ± 4 mmHg and 388 ± 11 vs. 367 ± 8 beats/min). Inhibition of the BK channel with 0.1 mg/kg of IBTX did not affect the response to Tempol (ΔMAP vehicle, −58 ± 6 vs. IBTX, −57 ± 6 mmHg, NS; and ΔHR vehicle, −43 ± 5 vs. IBTX, −36 ± 6 beats/min, NS). Higher doses of IBTX (0.3 mg/kg; n = 3) also did not alter the MAP or HR response to Tempol (ΔMAP vehicle, −67 ± 2 vs. IBTX −69 ± 5 mmHg; and ΔHR, −46 ± 11 vs. −40 ± 3 beats/min, NS). MAP and HR were similar in rats receiving vehicle or glibenclamide (172 ± 5 vs. 170 ± 5 mmHg and 377 ± 8 vs. 352 ± 6 beats/min, NS). Inhibition of KATP channels with glibenclamide (15 mg/kg iv) reduced the MAP but, in contrast to Tempol (Fig. 4). Cromakalim reduced the MAP but, in contrast to Tempol and hexamethonium, it led to reflex tachycardia (Fig. 5). Norepinephrine infused with cromakalim increased MAP but not to values of vehicle-treated rats (176 ± 6 vs. and 153 ± 5 mmHg, P < 0.05), although HR was similar (387 ± 6 vs. 374 ± 14 beats/min, NS). Pretreatment with cromakalim during norepinephrine blunted the MAP response to 174 μmol/kg of Tempol by 48% (ΔMAP, −56 ± 4 vs. −29 ± 3 mmHg, P < 0.01, n = 8) and blunted 50% of the bradycardia (ΔHR, −34 ± 5 vs. −17 ± 5 beats/min, P < 0.05; Fig. 6).

Series 4. Pretreatment with L-NAME (11 μmol·kg⁻¹·min⁻¹ iv) for 45 min increased the MAP (192 ± 5 vs. 166 ± 4 mmHg, P < 0.05), whereas HR was similar (363 ± 6 vs.
393 ± 8 beats/min, NS). L-NAME blunted the fall in MAP with 174 μmol/kg Tempol by 40% (ΔMAP vehicle −43 ± 6 vs. L-NAME −24 ± 3 mmHg; P < 0.01) without changing the bradycardia (ΔHR vehicle −49 ± 4 vs. L-NAME −41 ± 9 beats/min, NS). Inhibition of preganglionic neurotransmission with hexamethonium during infusion of norepinephrine led to a significant reduction in HR (365 ± 9 vs. 324 ± 13 beats/min, P < 0.01) but similar MAP (163 ± 3 vs. 161 ± 2 mmHg, NS). This pretreatment blunted the fall in MAP with Tempol by 40% (Fig. 7), which was strictly similar to that after L-NAME, although hexamethonium prevented changes in HR (ΔHR vehicle −24 ± 3 vs. L-NAME −24 ± 3 mmHg; P < 0.01). MAP and HR after combined pretreatment with L-NAME and hexamethonium (without norepinephrine) were rather lower than after the vehicle (164 ± 5 vs. 133 ± 11 mmHg, P < 0.05, and 404 ± 14 vs. 338 ± 15 beats/min, P < 0.05). This combined blockade of NOS and SNS blunted the fractional reduction in MAP with Tempol by 80% (Fig. 7). The effects of L-NAME and hexamethonium were fully additive (i.e., no interaction; Fig. 7). The combined pretreatment with hexamethonium and glibenclamide blunted the fall in MAP with Tempol by 58% (ΔMAP before −61 ± 5 vs. after −25 ± 3 mmHg; P < 0.01) and the fall in HR by 53% (ΔHR before −51 ± 7 vs. after −24 ± 3 beats/min; P < 0.01). The effects of glibenclamide and hexamethonium were less than additive (Fig. 7).

**Series 5.** The intracerebroventricular administration of Tempol, in doses of 1% to 10% of the effective intravenous dose, had no effects on MAP or HR, whereas the positive control ANG II raised the MAP (Fig. 8).

**DISCUSSION**

The main new findings are that the inhibition of catalase with 3-AT, infusion of PEG-catalase, inhibition of glutathione peroxidase with BSO alone or in combination with 3-AT, or inhibition of HO with SnMP does not blunt the acute response to Tempol. This suggests that this in vivo response does not relate to the generation of H₂O₂ or the activation of HO. Whereas the blockade of BK channels with IBTX is ineffective, the blockade of KATP channels with glibenclamide, or maintaining KATP channels open with an infusion of cromakalim during norepinephrine infusion to maintain the pretest BP, blunts 31% and 48% of the antihypertensive response to Tempol, respectively, thereby relating the response to Tempol in vivo to activation of KATP rather than to BK channels. We confirm the reports of Xu et al. (48, 49) and Shokoji et al. (40) that blockade of the SNS blunts 40% of the antihypertensive response to Tempol. Since intracerebroventricular administration of Tempol in doses of 1% to 10% of effective intravenous doses did not reduce the MAP, we conclude that Tempol acts predominantly on the peripheral SNS in our model. The block-
ade of NOS (39) blunts a similar fraction of the response as the blockade of the peripheral SNS. These two are fully additive, whereas the blockade of K<sub>ATP</sub> channels and the SNS are less than additive. We conclude that the inhibition of the peripheral SNS by Tempol is mediated in part via the opening of K<sub>ATP</sub> channels. Thus the antihypertensive response to Tempol is due to independent effects to potentiate NO and block the peripheral SNS in part via K<sub>ATP</sub> channels.

We have reported that the acute antihypertensive response among piperidine nitroxides is predicted by in vivo SOD mimetic activity (35). The finding that the response to Tempol was unaffected by PEG-catalase, 3-AT, or BSO suggests that the catalase-like activity of Tempol (22) may have prevented the accumulation of functionally significant quantities of H<sub>2</sub>O<sub>2</sub>. HO metabolizes heme to the antioxidant biliverdin and produces ferrous iron and the vasodilator CO (37). Our finding that SnMP did not modify the antihypertensive response to Tempol in the SHRs indicates that the antihypertensive actions of Tempol are not likely dependent on the activation of HO.

Tempol can reduce vascular O<sub>2</sub>•− and enhance NO bioactivity (52). We confirm the reports that the blockade of sympathetic ganglia (33) or NOS (39) reduces the acute antihypertensive response to Tempol. The finding that these effects on BP are additive is consistent with the conclusions of Xu et al. and Shokoji et al. that Tempol inhibits the SNS independent of NO (48). Since 80% of the antihypertensive response is blocked by hexamethonium + L-NAME, we conclude that the majority of the acute antihypertensive and bradycardic responses in vivo can be attributed to independent effects of Tempol on these systems. Prior reports of the effect of NOS inhibition on the antihypertensive response to Tempol range from complete blockade of the short-term response to Tempol in the SHRs (39) to a non-significant effect during more prolonged Tempol infusions (8).

BK channels are opened by H<sub>2</sub>O<sub>2</sub> on porcine coronary arteries (42) and by Tempol on VSMCs (47), apparently via an SOD-independent action (50). In contrast, we found no evidence that the fall in MAP with Tempol depends on H<sub>2</sub>O<sub>2</sub> or BK channels, since the responses were unaffected by changes in H<sub>2</sub>O<sub>2</sub> induced by PEG-catalase, 3-AT, or BSO or by the specific BK channel antagonist IBTX in a dose that blocks 55% of the acute antihypertensive action of nitroglycerine (1) or at a three times higher dose. On the other hand, activation of K<sub>ATP</sub> channels by cromakalim or the blockade of K<sub>ATP</sub> channels with glibenclamide blunted the fall in MAP with Tempol. We conclude that the activation of K<sub>ATP</sub> channels is more important than the activation of BK channels for the acute antihypertensive response to Tempol in vivo in the SHRs. This is consistent with reports that BK channels do not regulate renal vascular tone in vivo (28), whereas the activation of K<sub>ATP</sub> channels in anesthetized rats leads to potent dilation of the coronary and renal vascular beds (38), accompanied by a major fall in BP (Fig. 5). The observation that glibenclamide and hexamethonium are less than additive suggests that the site of the activation of K<sub>ATP</sub> channels by Tempol includes the SNS.

Fig. 5. Values are means ± SE changes in MAP (A) or HR (B) in rats given intravenous injection of Tempol (174 μmol/kg, n = 7 rat; single crosshatched bars), intravenous hexamethonium (Hex; 10 mg/kg, n = 10 rats; black bars), or intravenous cromakalim (98 μg/kg, n = 4 rats; gray bars).

Fig. 6. Values are means ± SE for changes in MAP (A) and HR (B) with intravenous injection of Tempol in rats pretreated with vehicle (solid symbols and continuous lines; n = 7 rats) or cromakalim (open symbols and broken lines; 50 μg iv bolus and 50 μg·kg<sup>−1</sup>·min<sup>−1</sup> for 15 min, n = 8 rats) with norepinephrine (1–3 μg·kg<sup>−1</sup>·min<sup>−1</sup>). The comparing groups are *P < 0.05 and **P < 0.01.
Indeed, KATP channels are expressed on sympathetic neurons (9) where their activation leads to hyperpolarization and neural inhibition (3, 34). Whereas H2O2 can activate KATP channels indirectly by depleting cells of ATP (12), it does not directly influence membrane KATP channels. However, these membrane KATP channels are inhibited by oxidation of thiols with O2•−/H2O2 (21) and activated by thiol antioxidants such as N-acetyl-L-cysteine (43), likely reflecting the critical role of a redox-sensitive thiol in the active site (6). Thus Tempol could activate membrane KATP channels by reducing O2•− and thereby reversing thiol oxidation.

KATP channels are also expressed in vascular endothelium (15, 18). Opening of endothelial KATP channels by Tempol should hyperpolarize these cells and might thereby increase the intracellular calcium concentration and activate NOS (26, 27). However, Katnik and Adams (17) demonstrate that the opening of KATP channels with levcromakalim in rabbit arterial endothelium does not significantly change intracellular calcium concentration. Herrera et al. (14) also report that cromakalim has no effect on endothelial NO generation or intracellular calcium levels in cultured rat pulmonary endothelial cells and that inhibition of NOS does not modify the fall in BP with cromakalim in conscious rats and the vasodilation in isolated perfused tail arteries from rats. Therefore, the opening of KATP channels likely does hyperpolarize endothelial cells, but this is not necessarily accompanied by an increase in intracellular calcium or NOS activity. We conclude that it is unlikely that the blockade of the antihypertensive response to Tempol by intravenous cromakalim in our study is due to increased endothelial cell NO generation, but this has not been investigated directly by us.

The finding that hexamethonium blunts the response to Tempol implies an action of Tempol on SNS at, or proximal to, the ganglion. The central nervous system administration of Tempol inhibits hypothalamic norepinephrine release and reduces the MAP of normotensive rats (4). In contrast, we found that graded intracerebroventricular injections of Tempol across a range (0.2–5.1 μmol/kg) that would not reduce MAP if Tempol escaped into the systemic circulation were ineffective. Our findings are consistent with the report of Shokoji et al. (40) that intracerebroventricular infusion of 1 μmol of Tempol over 1 min does not affect the MAP or renal sympathetic nerve activity of anesthetized SHRs or Wistar-Kyoto rats.

Limitations of this study include the testing of Tempol only in the SHR model, the use of acute dosing of Tempol, and the use of doses of inhibitors based on prior reports in the literature without retesting the effectiveness of each in the model used for this study.

In conclusion, the acute antihypertensive response to Tempol in the anesthetized SHRs depends on the independent effects to
increase NO bioactivity and to depress the peripheral SNS due in part to the opening of KATP channels.

PERPECTIVES

An abrupt reduction in BP during infusion of sodium nitroprusside (2) or cromakalim (Fig. 5) activates the SNS. This can increase cardiac energy demands, induce arrhythmias, stimulate catecholamine release from pheochromocytomas, and augment the shear force on the vessel wall that predisposes to extension of an acute aortic dissection (29). Tempol, which elicits dose-dependent, abrupt, and rapidly reversible reductions in MAP while simultaneously reducing the HR and SNS activity when administered acutely, could have a distinct advantage as therapy for patients with hypertensive crises or hypertensive patients with coronary insufficiency at risk for arrhythmias. Tempol reduces MAP, whether given as an intravenous injection, a constant infusion (39), or by addition to the drinking water (45). Moreover, prolonged administration of Tempol corrects salt sensitivity in hypertensive models (45), whereas acute Tempol increases diuresis and natriuresis in rats drinking water (45). Moreover, prolonged administration of Tempol reduces MAP, whether given as an intravenous injection, a constant infusion (39), or by addition to the drinking water (45). Moreover, prolonged administration of Tempol corrects salt sensitivity in hypertensive models (45).}

ACKNOWLEDGMENTS

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