

Endothelin 1–Dependent Neurovascular Dysfunction in Chronic Intermittent Hypoxia

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See Editorial Commentary, pp 22–24

Abstract—Obstructive sleep apnea, a condition resulting in chronic intermittent hypoxia (CIH), is an independent risk factor for stroke and dementia, but the mechanisms of the effect are unknown. We tested the hypothesis that CIH increases cerebrovascular risk by altering critical mechanisms regulating cerebral blood flow thereby lowering cerebrovascular reserves. Male C57Bl6/J mice were subjected to CIH (10% O₂ for 90 seconds/room air for 90 seconds; during sleep hours) or sham treatment for 35 days. Somatosensory cortex blood flow was assessed by laser Doppler flowmetry in anesthetized mice equipped with a cranial window. CIH increased mean arterial pressure (from 74±2 to 83±3 mm Hg; $P<0.05$) and attenuated the blood flow increase produced by neural activity (whisker stimulation; $-39\pm2\%$; $P<0.05$) or neocortical application of endothelium-dependent vasodilators (acetylcholine response: $-41\pm3\%$; $P<0.05$). The cerebrovascular dysfunction was associated with oxidative stress in cerebral resistance arterioles and was abrogated by free radical scavenging or NADPH oxidase inhibition. Furthermore, cerebrovascular dysfunction and free radical increase were not observed in mice lacking the NOX2 subunit of NADPH oxidase. CIH markedly increased endothelin 1 in cerebral blood vessels, whereas cerebrovascular dysfunction and oxidative stress were abrogated by neocortical application of the endothelin type A receptor antagonist BQ123. These data demonstrate for the first time that CIH alters key regulatory mechanisms of the cerebral circulation through endothelin 1 and NADPH oxidase–derived radicals. The ensuing cerebrovascular dysfunction may increase stroke risk in patients with sleep apnea by reducing cerebrovascular reserves and increasing the brain’s susceptibility to cerebral ischemia. (*Hypertension*. 2012;60:106-113.) • [Online Data Supplement](#)

Key Words: obstructive sleep apnea ■ reactive oxygen species ■ neurovascular coupling
■ endothelium-dependent vasodilation

Obstructive sleep apnea (OSA) is a highly prevalent condition characterized by recurring apneic episodes during sleep resulting in intermittent hypoxia, increased intrathoracic pressure, and arousal.¹ OSA is associated with an increased risk for cardiovascular diseases, including stroke.² Longitudinal studies have firmly established that moderate or severe OSA (≥ 20 apneic events per hour) is an independent risk factor for stroke.^{3,4} Moreover, OSA is associated with vascular cognitive impairment⁵ and Alzheimer disease,⁶ suggesting that OSA may also increase the susceptibility of the brain to cognitive dysfunction and dementia.

OSA exerts deleterious effects on systemic blood vessels.¹ Thus, OSA impairs endothelial-dependent relaxation, induces

arterial stiffness, and promotes inflammation and atherosclerosis.^{7,8} However, little is known about the effects of OSA on the cerebral circulation and, particularly, on its impact on critical mechanisms regulating cerebrovascular function. Chronic intermittent hypoxia (CIH), which recapitulates selected feature of OSA, is widely used as a model of OSA.⁹ A single study in isolated middle cerebral arteries found that CIH impairs endothelium-dependent relaxation and attenuates the vasodilatation produced by hypoxia.¹⁰ Although these in vitro findings suggest that CIH has an impact on cerebral blood vessels, it remains to be established whether CIH alters the dynamic regulation of cerebral blood flow (CBF) in vivo and the mechanisms involved. In addition, clinical studies using mainly flow velocity as an index of

Received February 27, 2012; first decision May 11, 2012; revision accepted May 7, 2012.

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The online-only Data Supplement is available with this article at <http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.112.193672/-/DC1>.

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Hypertension is available at <http://hyper.ahajournals.org>

DOI: 10.1161/HYPERTENSIONAHA.112.193672

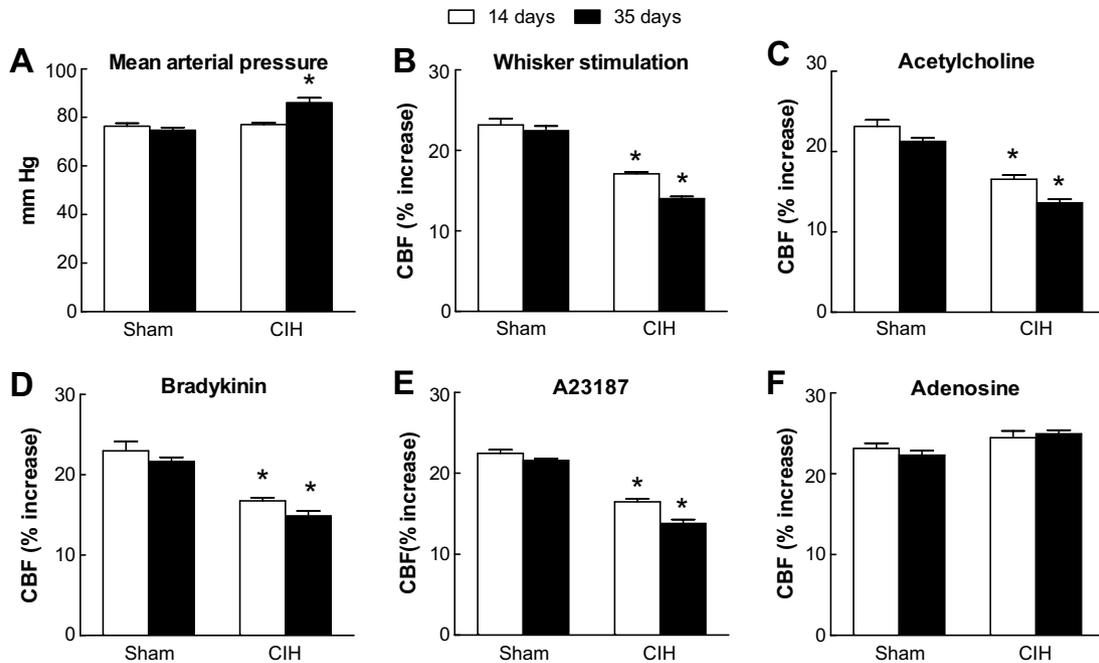


Figure 1. Chronic intermittent hypoxia (CIH) increases mean arterial pressure (MAP; **A**) and attenuates the increase in cerebral blood flow (CBF) produced by whisker stimulation (**B**), acetylcholine (ACh; **C**), bradykinin (**D**), and A23187 (**E**) but not adenosine (**F**). Note that the cerebrovascular effects are already present at 14 days, when MAP is not elevated. * $P < 0.05$ from respective sham group, ANOVA and Tukey test; $n = 5$ per group; □, 14 days; ■, 35 days.

CBF have raised the possibility that OSA and CIH alter the cerebral circulation.² However, the specific role of CIH in these alterations remains uncertain because of comorbid conditions, such as aging, obesity, hypertension, and diabetes mellitus, that also impair cerebrovascular regulation.^{11–13} Therefore, there is a wide knowledge gap regarding the effect of CIH on critical mechanisms regulating the cerebral circulation, the failure of which may increase the brain's susceptibility to ischemic injury.

In this study, we sought to determine whether CIH alters the regulation of the cerebral circulation and, if so, to elucidate the mechanisms and mediators of the effects. Using a mouse model we demonstrated for the first time that CIH induces a profound disruption of vital mechanisms through which endothelial cells and neural activity regulate CBF. The effect is mediated by NADPH oxidase–dependent vascular oxidative stress triggered by the potent vasoactive peptide endothelin 1 (ET1). The findings establish that CIH, a key pathogenic factor in OSA, alters critical regulatory mechanisms of the cerebral circulation, which may reduce vascular reserves and contribute to the increased risk for stroke and dementia observed in this condition.

Methods

All of the methods used in this study have been described in detail in previous publications from this laboratory,^{14–19} and are briefly summarized. All of the procedures were approved by the institutional animal care and use committee of Weill Cornell Medical College.

Mice

Studies were conducted in 3-month-old male mice (weight, 27–30 g). C57Bl6/J and NOX2^{−/−} mice were obtained from in house

colonies.¹⁷ NOX2^{−/−} mice were congenic with the C57Bl6 strain, and C57Bl6/J mice were used as wild-type controls.

CIH

CIH was induced as described previously using a custom system designed by Dr George J. Delagrammatikas.¹⁹ Briefly, mice were randomly assigned to CIH or sham groups. Oxygen (O₂) levels within the animals' cage were changed from normal (21 ± 1%) to low (10 ± 1%) for 90 seconds every 90 seconds, resulting in 20 hypoxic episodes per hour.¹⁹ The cages of sham-treated mice were infused with room air for 90 seconds every 90 seconds. The cycling hypoxia was induced for 8 hours during the light (sleep) phase (8:00 am to 4:00 pm). This procedure results in cyclic reduction in O₂ saturations comparable to those observed in OSA (see Reference 19 for blood gases). During the remaining 16 hours of the day (4:00 pm to 8:00 am), both CIH and control cages were infused with room air. CIH and sham protocols were repeated for 14 or 35 days, during which the mice had free access to food and water.

General Surgical Procedures and CBF Measurement

Mice were anesthetized with isoflurane, intubated, and artificially ventilated (SAR-830, CWE Inc.).^{14,16} Mean arterial pressure (MAP), rectal temperature, and blood gases were monitored and controlled.^{14,16} After surgery, anesthesia was maintained with urethane (750 mg/kg IP) and chloralose (50 mg/kg IP).^{14,16} CBF was monitored with a laser-Doppler probe (Periflux System 5010, Perimed AB) in a cranial window overlying the somatosensory cortex.¹⁴ CBF was expressed as percentage increases relative to the resting level.

Experimental Protocol for CBF Experiments

After MAP and blood gases were stable (Pco₂, 33–36 mm Hg; Po₂, 120–130 mm Hg; pH 7.3–7.4), the cranial window was superfused with Ringer solution (vehicle) and CBF responses were recorded.^{14–16} The whisker-barrel cortex was activated for 60 sec-

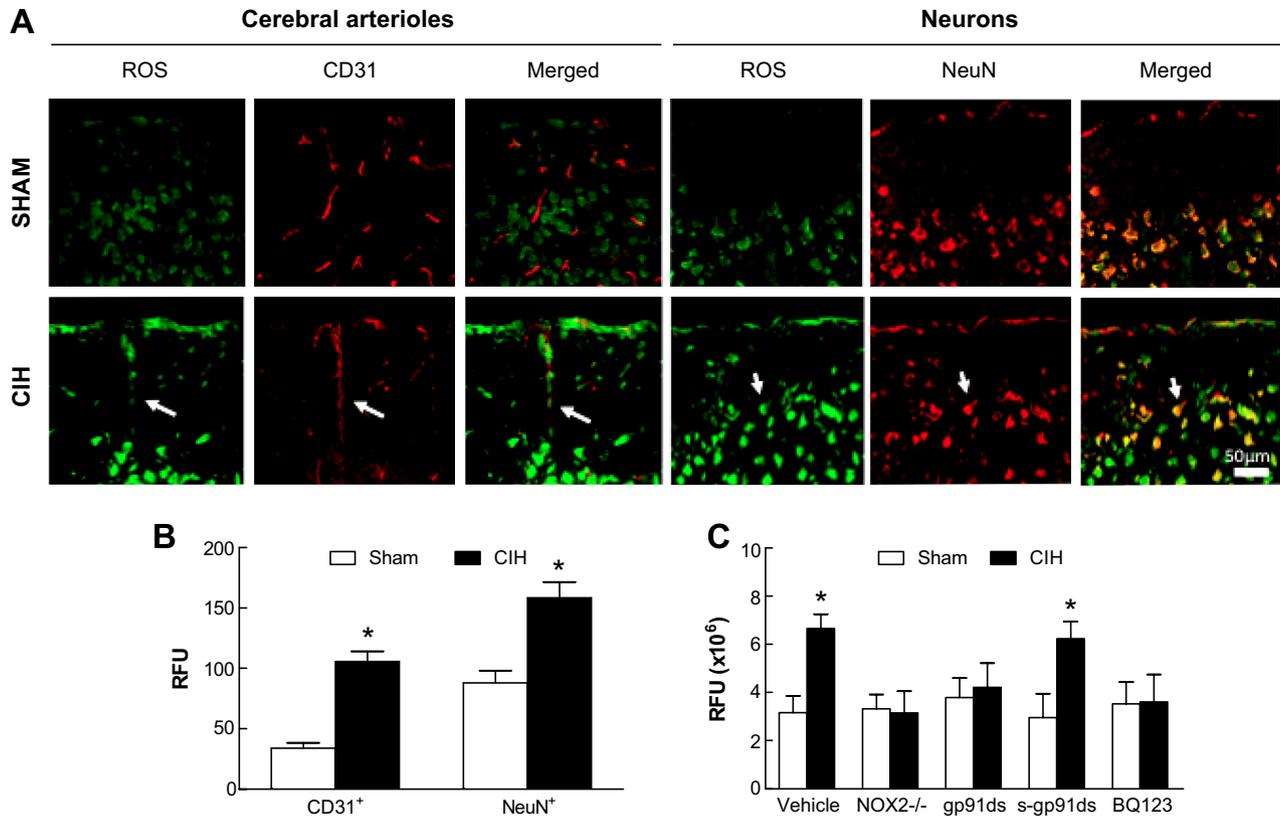


Figure 2. Chronic intermittent hypoxia (CIH; 35 days) increases reactive oxygen species (ROS) in blood vessels (CD31⁺) and neurons (NeuN⁺) of the somatosensory cortex (**A** and **B**). The ROS increase is not observed in NOX2^{-/-} mice and is suppressed by gp91ds-tat (gp91ds) or BQ123 but not by a scrambled gp91ds peptide (s-gp91ds; **C**); **P*<0.05 from sham group; n=5 per group. □, sham; ■, CIH.

onds by stroking the contralateral vibrissae,¹⁶ and the evoked changes in CBF were recorded. The endothelium-dependent vasodilators acetylcholine (ACh; 10 μ mol/L; Sigma) and bradykinin (50 μ mol/L; Sigma) and the calcium ionophore A23176 (3 μ mol/L; Sigma) or the smooth muscle relaxant adenosine (400 μ mol/L; Sigma) were superfused on the exposed neocortex for 5 minutes. In some studies, CBF responses were tested with vehicle superfusion or after 30 minutes of superfusion with the reactive oxygen species (ROS) scavenger Mn(III)tetrakis(4-benzoic acid)porphyrin Chloride (MnTBAP; 100 μ mol/L; Calbiochem)¹⁶ the ET_A receptor (ET_AR) antagonist BQ123 (1 μ mol/L; Tocris),²⁰ the angiotensin II type 1 receptor antagonist losartan (10 μ mol/L; Sigma),¹⁶ the NADPH oxidase peptide inhibitor gp91ds-tat (1 μ mol/L),^{16,17} or the scrambled control peptide (1 μ mol/L), all dissolved in Ringer.

Immunohistochemistry

Coronal brain sections were cut through the somatosensory cortex using a cryostat and incubated, after antigen retrieval, with primary antibodies against ET1 (1:250; Peninsula Laboratory). After incubation with a secondary antibody, sections were mounted on slides and examined using a Leica confocal microscope.^{15,18} The specificity of the immunofluorescence was verified in pilot studies by omission of the primary antibody and by preabsorption with the antigen.

ROS Detection

ROS production was assessed by dihydroethidium (DHE) microfluorography.^{17,18} DHE was topically superfused on the somatosensory cortex for 60 minutes. Ringer solution containing DHE or DHE plus BQ123, gp91ds-tat, or the control peptide was superfused. Mice were killed 30 to 40 minutes later, coronal brain sections were cut through the neocortex underlying the cranial window, and ROS was

determined as described previously.^{17,18} In some experiments, the cellular source of the ROS signal was assessed by immunostaining the brain sections for the endothelial marker CD31 (1:200; BD Pharmingen) or the neuronal marker NeuN (1:200).^{15,18} The intensity of the cell-specific ROS signal was quantified by confocal microscopy, as described previously.¹⁵

RT-PCR and ET1 ELISA

Cerebral blood vessels were isolated from the brain surface by stripping the pia mater and homogenizing and purifying over C18 columns.¹⁸ ET1 was measured using a commercially available ELISA kit (Enzo Life Sciences). Because the mRNA for ET1 is unstable,²¹ we assessed the vascular expression of the endothelin-converting enzyme 1 (ECE-1), a protease that cleaves big ET1 into ET1, using RT-PCR. Primers were 5'-GCCTACCGGGCGTACCAGAAC-3' and 5'-GGTGTGCGGAC-AGAGCACCAG-3'. We also assessed the expression of ET_AR and ET_BR in pial preparation. Primers were 5'-TCGAGAAGTG-GCAAAGACTGT-3' and 5'-CACCGGTTCTTATCCATCTCA-3' for ET_AR and 5'-AAGCAGTCCTTGGAGGAGAAG-3' and 3'-ATTTATTGCTGGACCGGAAGT-5' for ET_BR. ECE-1, ET_AR, and ET_BR mRNA levels were normalized to hypoxanthine phosphoribosyl-transferase mRNA, and relative expression levels were calculated as described.¹⁸

Data Analysis

Data are expressed as mean \pm SEM. Two group comparisons were evaluated using the Student *t* test. Multiple comparisons were evaluated by the ANOVA and Tukey test. Differences were considered statistically significant for *P*<0.05.

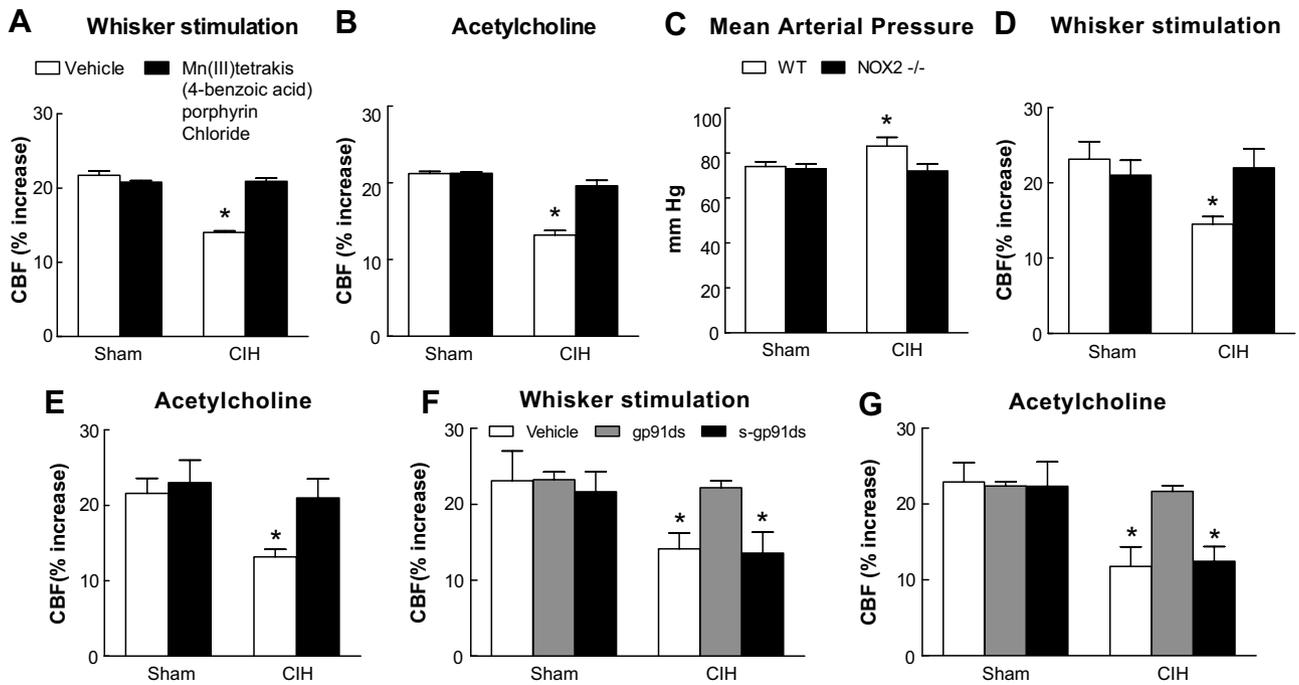


Figure 3. The reactive oxygen species (ROS) scavenger Mn(III)tetrakis(4-benzoic acid)porphyrin Chloride reverses the chronic intermittent hypoxia (CIH)-induced suppression of the cerebral blood flow (CBF) response to whisker stimulation (**A**) or acetylcholine (ACh; **B**). CIH does not increase mean arterial pressure (**C**) and does not alter CBF responses to whisker stimulation (**D**) or ACh (**E**) in $\text{NOX2}^{-/-}$ mice. The NADPH oxidase peptide inhibitor gp91ds-tat (gp91ds) but not its scrambled control (s-gp91ds) reverses the CIH-induced attenuation of CBF response to whisker stimulation (**F**) or ACh (**G**). * $P < 0.05$ from respective sham group; $n = 5$ per group. **A** and **B**, □, vehicle; ■, Mn(III)tetrakis(4-benzoic acid)porphyrin Chloride. **C** through **E**, □, wild-type (WT); ■, $\text{NOX2}^{-/-}$; **F** and **G**, □, vehicle; ■, gp91ds; ▨, s-gp91ds.

Results

CIH Alters Neurovascular Coupling and Endothelium-Dependent Responses in the Somatosensory Cortex

As reported previously,¹⁹ CIH increased blood pressure in awake (Figure S1A and S1B, please see the online-only Data Supplement) and anesthetized mice (Figure 1A) at 35 but not 14 days. However, CIH attenuated the increase in CBF induced by whisker stimulation both at 14 and 35 days (Figure 1B). Endothelium-dependent response to ACh and to bradykinin and A23187 were also attenuated (Figure 1C through 1E). In contrast, the increase in CBF induced by the smooth muscle relaxant adenosine was not reduced (Figure 1F), suggesting that CIH did not alter the ability of smooth muscle cells to relax.

NADPH Oxidase-Derived ROS Are Involved in the Cerebrovascular Effects of CIH

Next, we examined the mechanisms of the neurovascular dysfunction induced by CIH. Vascular oxidative stress is well known to induce alterations in cerebrovascular regulation.²² Therefore, we examined whether CIH increases ROS production in the neocortex in which CBF was measured. CIH (35 days) markedly increased ROS production, assessed by DHE microfluorography (Figure 2A). The ROS increase was observed both in CD31-positive somatosensory cortex arterioles and in NeuN-positive neurons (Figure 2A). Neocortical superfusion with the ROS scavenger Mn(III)tetrakis(4-benzoic acid)

porphyrin Chloride did not alter resting CBF (CIH mice: vehicle, 21 ± 3 perfusion units; Mn(III)tetrakis(4-benzoic acid)porphyrin Chloride, 22 ± 4 perfusion units; $P > 0.05$) or the MAP elevation (Figure S2A), but it completely reversed the attenuation in the CBF response to whisker stimulation and ACh (Figure 3A and 3B). An NOX2-containing NADPH oxidase is involved in the cerebrovascular dysfunction in several models of vascular oxidative stress.^{16,17,22} Therefore, we used NOX2-null mice to examine whether NOX2 is involved in the cerebrovascular alterations induced by CIH. CIH did not increase MAP and did not induce oxidative stress or cerebrovascular dysfunction in NOX2-null mice (Figure 2C and 3C through 3E). To determine whether NADPH oxidase was responsible for ROS generation in the neocortex where CBF was monitored, we used neocortical superfusion of the peptide inhibitor gp91ds-tat.^{16,17} gp91ds-tat, but not its scrambled control, completely reversed the oxidative stress and cerebrovascular dysfunction induced by CIH (Figure 2C and 3F and 3G), without affecting MAP or the CBF response to adenosine (Figure S2C, D). These observations indicate that local generation of NADPH oxidase-derived ROS plays a role in the neurovascular dysfunction induced by CIH.

Neurovascular Dysfunction and Oxidative Stress Are Reversed by the ET_A Antagonist BQ123

Angiotensin II and ET1 are potent vasoactive peptides that induce vascular oxidative stress, have powerful effects on cerebral blood vessels, and have been implicated in CIH.^{11,23–25} Therefore, we investigated whether angiotensin

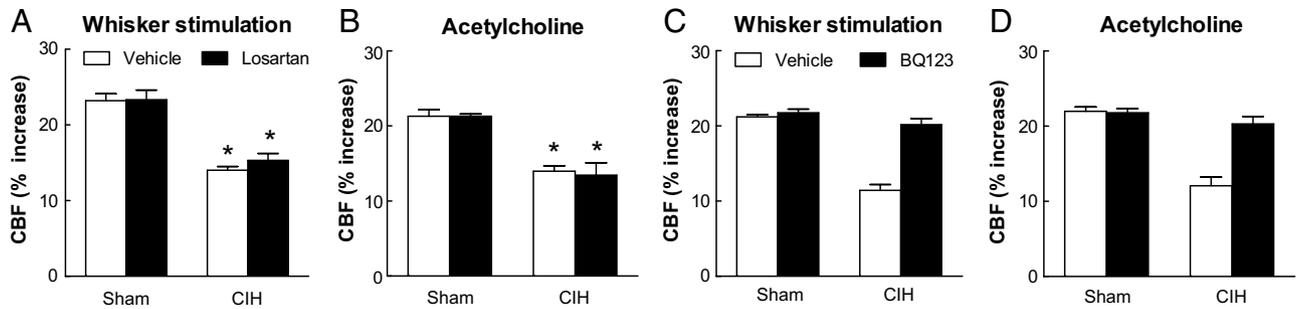


Figure 4. Losartan does not rescue the chronic intermittent hypoxia (CIH)-induced attenuation of the cerebral blood flow (CBF) response to whisker stimulation (A, □, vehicle; ■, losartan) or acetylcholine (ACh; B, □, vehicle; ■, BQ123), whereas BQ123 rescues the dysfunction in full (C and D). * $P < 0.05$ from respective sham group; $n = 5$ per group.

II or ET1 contributes to the alterations in cerebrovascular regulation induced by CIH. Topical neocortical application of the angiotensin II type 1 receptor antagonist losartan, at a concentration effective in counteracting the effects of angiotensin II in this preparation ($10 \mu\text{mol/L}$),¹⁶ did not reverse the neurovascular dysfunction (Figure 4A and 4B). In contrast, topical application of the ET_AR antagonist BQ123 ($1 \mu\text{mol/L}$) counteracted fully the attenuation of the CBF responses to whisker stimulation and ACh induced by CIH (Figure 4C and 4D). BQ123 did not affect resting CBF (CIH mice: vehicle, 21 ± 3 perfusion units; BQ123, 22 ± 4 perfusion units; $P > 0.05$), the elevation in CBF induced by adenosine, and the MAP elevations induced by CIH (Figure S2G and S2H). However, BQ123 superfusion blocked the ROS increase (Figure 2C), implicating ET_A in the vascular oxidative stress induced by CIH.

Neurovascular Dysfunction Is Associated With Cerebrovascular Upregulation of ET1

We then sought to determine whether CIH upregulates ET1 in the pial arterioles responsible for the CBF increase. ET1 immunofluorescence was increased in neocortical cerebral arterioles of the somatosensory cortex in association with the endothelial marker CD31 (Figure 5A). Measurements of ET1 in pial vascular preparations revealed a marked increase of this peptide after CIH (Figure 5B). Plasma ET1 at 35 days of CIH was below the level of detection of the assay. The ET1 increase was associated with elevation of the ET1 synthetic enzyme ECE-1 mRNA (Figure 5C), suggesting local production of ET1. Furthermore, CIH increased the mRNA expression of ET_A but not ET_B receptors (Figure 5D and 5E).

Discussion

Novel Findings of the Study

Our results provide the first evidence that CIH, a key pathogenic factor in OSA, induces profound alterations of cerebrovascular regulation involving not only endothelium-dependent vasodilation (ACh, bradykinin, and A23197) but also neurovascular coupling. Because the CBF response to ACh is mediated by NO, whereas that to bradykinin and A23197 is mediated by cyclooxygenase reaction products,^{14,26} the data indicate a broad disruption of endothelial dependent vasoactivity. Moreover, the attenuation in

endothelium-dependent responses involves both receptor-dependent (ACh and bradykinin) and receptor-independent agonists (A23187), indicating that the effect is not because of receptor alterations. The vascular dysfunction is associated with an increase in vascular ROS, is reversed by a ROS

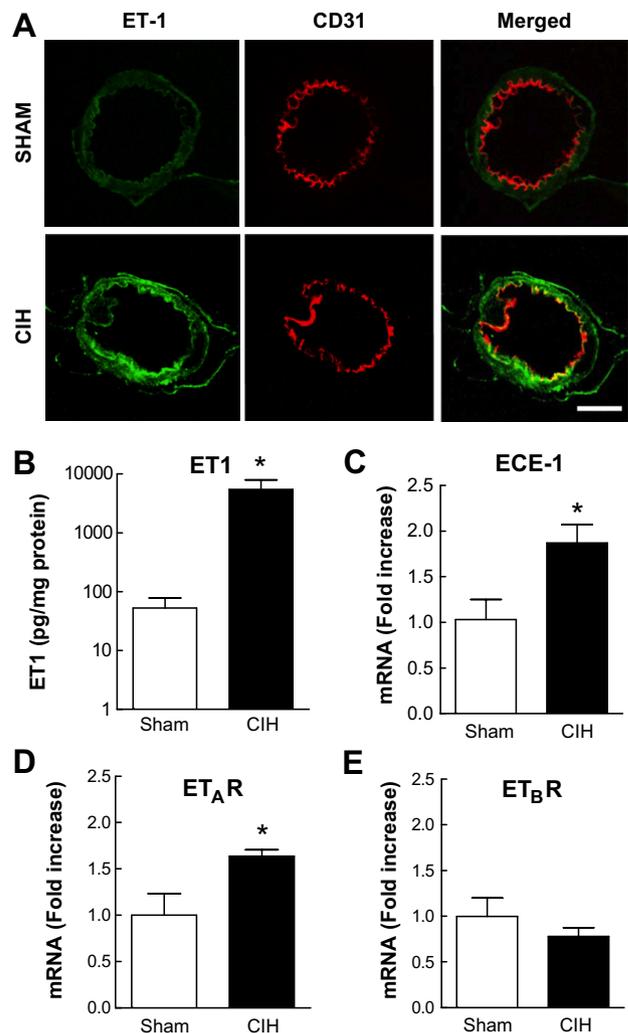


Figure 5. Chronic intermittent hypoxia (CIH) increases endothelin (ET) 1 immunoreactivity in CD31⁺ pial arterioles of the somatosensory cortex (A). CIH increases ET1, assessed by ELISA (B), as well as endothelin-converting enzyme 1 (ECE-1; C), ET_A (D), and ET_B (E) receptor mRNA in pial vessels preparations. * $P < 0.05$ from sham group; $n = 5$ per group.

scavenger or an NADPH oxidase inhibitor, and is not observed in NOX2 null mice. Furthermore, the dysfunction is associated with marked increase in ET1 and ET_AR in pial arterioles and is abrogated by acute application of the ET_AR antagonist BQ123 but not by the angiotensin II type 1 receptor antagonist losartan. ET_AR inhibition also dampens the increase in vascular ROS produced by CIH. These observations collectively demonstrate that CIH is associated with a profound alteration of critical mechanisms regulating the cerebral circulation and that vascular oxidative stress, ET1, and ET_AR are involved in its mechanisms.

Methodologic Considerations

Animal models of OSA reproduce some but not all aspects of this condition, and each model has advantages and disadvantages.⁹ Although CIH does not mimic all of the features of OSA, for example, sleep fragmentation and increases in intrathoracic pressure, a large body of literature indicates that CIH reproduces the key vascular correlates of OSA.^{1,9} Thus, CIH is considered highly predictive of the cardiovascular effects of OSA and, as such, is the standard of the field for studies of OSA.^{1,9} Furthermore, the findings of the present study cannot be attributed to differences in the physiological parameters of the mice because MAP and blood gases were monitored and carefully controlled. Similarly, the reversal of the CIH-induced attenuation of CBF responses by BQ123, Mn(III)tetrakis(4-benzoic acid)porphyrin Chloride, or gp91ds-tat is not the result of a nonspecific enhancement of vascular reactivity, because the response to the smooth muscle relaxant adenosine was not enhanced.

ROS Are Involved in the Cerebrovascular Alterations Induced by CIH

We found that CIH increases ROS production in cerebral blood vessels and neurons. Furthermore, ROS scavengers attenuate the ROS signal and counteract the attenuation in functional hyperemia and endothelial-dependent responses, indicating that the cerebrovascular dysfunction is attributable to oxidative stress. The mechanisms by which oxidative stress induces cerebrovascular dysfunction have not been completely elucidated but may include depletion of NO and, possibly, changes in the production of prostanoids,²⁷ factors involved both in functional hyperemia and endothelium-dependent responses.^{22,26} Our finding that the ROS increase is absent in NOX2 null mice implicates a NOX2-containing NADPH oxidase as a source of the ROS. However, NOX2 is also involved in the central oxygen sensing that initiates the cardiovascular effects of CIH,²⁸ consistent with our observation that CIH did not increase MAP in NOX2-null mice. Therefore, lack of cerebrovascular dysfunction in NOX2-null mice cannot be attributed necessarily to a reduction in neocortical ROS. However, neocortical application of the peptide inhibitor gp91ds-tat completely reverses the dysfunction, implicating local NADPH oxidase-derived ROS in its mechanisms. Therefore, as in models of hypertension, diabetes mellitus, aging, hyperlipidemia, and β -amyloid accumulation,²² NADPH oxidase is also involved in the cerebrovascular dysfunction induced by CIH.

These observations, collectively, highlight the critical importance of NADPH oxidase as a mediator of oxidative stress in a wide variety of conditions associated with cerebrovascular dysfunction.

ET1, Through ET_AR, Is Responsible for Both Oxidative Stress and Cerebrovascular Alterations

Another major finding of the present study is that the vascular oxidative stress and cerebrovascular dysfunction induced by CIH are mediated by ET1 via ET_AR, which, unlike ET_B, are upregulated by CIH. ET1 is a potent constrictor of cerebral blood vessels,²³ but its effects on the mechanisms regulating the cerebral circulation have not been studied extensively. We found that ET1 can account for both the alterations in functional hyperemia and endothelial-dependent responses induced by CIH. The effect of ET1 is mediated through production of ROS generated by NADPH oxidase, an enzyme well known to be activated by ET1.²⁹ In contrast, acute inhibition of angiotensin II type 1 receptors did not restore cerebrovascular function, but we cannot rule out whether chronic inhibition during CIH would be effective. Therefore, our data suggest that ET1 is involved in the cerebrovascular alterations induced by CIH. The observation that BQ123 does not increase resting CBF in mice subjected to CIH is consistent with the hypothesis that the increase in cerebrovascular ET1 does not reduce resting CBF, but quantitative CBF measurements would be needed to establish this point more firmly. The mechanisms of the vascular ET1 increase remain to be defined. Because ET1 and ECE-1 are hypoxia-inducible factor 1 α -dependent genes,³⁰ one likely possibility is that activation of this transcription factor, which has been reported in CIH,³¹ is responsible for the ET1 upregulation. Furthermore, the increase in ECE-1 in pial vascular preparations suggests local vascular ET1 production. Additional studies will be required to elucidate the molecular mechanisms of ET1 expression in cerebral blood vessels during CIH and the roles of ECE-1 and possibly ET_BR in the dysfunction.

Potential Implications for OSA and Associated Increased Stroke Risk

OSA has emerged as an independent risk factor for stroke and dementia. Recent longitudinal studies have firmly established that moderate or severe OSA increases stroke risk by \approx 3-fold.^{3,4} Asymptomatic ischemic lesions (silent strokes) are particularly frequent in OSA,³² and undiagnosed OSA has been implicated in patients in whom the cause of stroke cannot be ascertained (cryptogenic strokes).³³ The present results provide insight into the mechanistic bases for the increased cerebrovascular risk in OSA, which may be attributed to a reduced capacity of the cerebrovascular bed to compensate for vascular occlusion, that is, reduced cerebrovascular reserves. After occlusion of a cerebral artery, collateral flow arising from adjacent vascular districts is essential for the survival of the brain tissue at the periphery of the ischemic territory, the so-called ischemic penumbra.³⁴ The formation of an effective collateral circulation depends on cerebrovascular regulatory mechanisms that, through vasodi-

lation, redirect flow toward the ischemic zone.³⁵ Considering that alterations in endothelium-dependent responses and/or neurovascular coupling reduce collateral flow and exacerbate focal cerebral ischemic injury,^{36,37} the cerebrovascular dysfunction induced by CIH could increase the susceptibility of the brain to ischemic injury by a similar mechanism. Therefore, the present results provide the first evidence to date that CIH is sufficient to alter critical regulatory mechanisms of the cerebral circulation, the disruption of which is known to increase the susceptibility of the brain to ischemic injury and neurodegeneration.³⁸ Our findings also identify ET_AR as a potential therapeutic target for the cerebrovascular dysfunction induced by CIH. ET_A antagonists are currently in clinical use,³⁹ and their use in OSA would be feasible.

Perspectives

We have demonstrated that CIH, a key pathogenic factor in OSA, is associated with a profound disruption of critical mechanisms regulating the cerebral circulation. The effect depends on NADPH oxidase-derived ROS triggered by a marked increase in ET1 in cerebral resistance arterioles. Accordingly, an ET_AR antagonist suppresses CIH-induced ROS production and completely reverses the cerebrovascular alterations. Considering that cerebrovascular dysfunction increases the brain's susceptibility to ischemic injury and neurodegeneration, the findings provide insight into the increased risk for stroke and dementia observed in patients with OSA and suggest that ET_AR antagonists may be potentially beneficial in this condition.

Sources of Funding

This work was supported by National Institutes of Health grants HL96571 and NS73666.

Disclosures

None.

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Novelty and Significance

What Is New?

- CIH alters critical cerebrovascular regulatory mechanisms.
- The effect is mediated by NADPH oxidase–derived ROS.
- Endothelin 1 and ET_AR are responsible for the ROS increase and the cerebrovascular dysfunction.

What Is Relevant?

- CIH is a key pathogenic factor in obstructive sleep apnea, a condition associated with an elevated risk for stroke and dementia.
- CIH-induced cerebrovascular dysfunction may increase the susceptibility of the brain to ischemic injury by compromising the ability of the cerebrovascular bed to compensate for the ischemia induced by arterial occlusion (cerebrovascular reserves).

- ET_AR antagonists are potentially useful to reverse the cerebrovascular abnormalities.

Summary

The finding that CIH alters cerebrovascular function provides the mechanistic bases for the reduced vascular reserves and increased susceptibility to ischemic injury associated with obstructive sleep apnea. The involvement of ET_AR and radicals suggests new therapeutic approaches to counteract the deleterious cerebrovascular effects of OSA.