Intermittent hypoxia causes mandibular growth retardation and macroglossia in growing rats

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Introduction: In this study, we aimed to examine the role of intermittent hypoxia (IH) in dentofacial morphologic changes in growing rats. **Methods:** Seven-week-old male rats were exposed to IH at 20 cycles per hour (nadir of 4% oxygen to peak of 21% oxygen) for 8 hours per day for 6 weeks. Control rats were exposed to normoxia (N). Maxillofacial growth was compared between the 2 groups by linear measurements on cephalometric radiographs. To examine the dental arch morphology, study models and microcomputed tomography images of the jaws were taken. Additionally, tongue size was measured. **Results:** The gonial angle and the ramus of the mandible were smaller in the IH group than in the N group, whereas the body weights were not different between the 2 groups. Morphometric analysis of the dentition showed a significantly wider mandibular dentition and narrower maxillary dentition in the IH than in the N group. The relative width (+4.2 %) and length (tongue apex to vallate papillae, +3.5 %) of the tongue to the mandible were significantly greater in the IH group than in the N group. **Conclusions:** IH induced dentofacial morphologic discrepancies in growing rats. (Am J Orthod Dentofacial Orthop 2017;151:363-71)

Anatomic imbalances between the upper airway soft tissues and the craniofacial dimensions, a lower hyoid bone position, and abnormal upper airway neuromotor tone have been implicated in the development of obstructive sleep apnea (OSA) in children.[1] Children at high risk for sleep-disordered breathing exhibit mandibular retrognathia with a palatal crossbite and narrowed dentoalveolar transverse width in the maxillary dental arch. These dentofacial characteristics are associated with reduced nasopharyngeal and oropharyngeal sagittal dimensions.[2] Additionally, distinct correlations have been shown among maxillary constriction, nasal air resistance, and OSA severity.[3] The effectiveness of various corrective measures for dentofacial morphologic changes in children with OSA has demonstrated that such morphologic changes contribute to the development and progression of OSA.[4] Hyoid-mandibular narrowing and tongue enlargement predict the severity of OSA and the likelihood of its treatability by continuous positive airway pressure in patients.[5] Moreover, hypertrophy of the tongue base and root can induce pharyngeal obstruction, which can be treated with radiofrequency volumetric tissue reduction of the tongue.[6]

Pediatric OSA is a multifactorial disorder with a variety of causes, including obesity and related metabolic diseases, prematurity, nasal abnormalities, and adenotonsillar hypertrophy.[7,8] In adults, the most common cause of OSA is obesity associated with excessive soft tissues in the mouth and throat areas. Obesity is also associated with an increase in the systemic inflammation commonly found in children with OSA.[9] However, OSA in the nonobese population is often reported in children and adults.[10-12] Thus, pediatric OSA is not necessarily restricted to obese children. Although childhood obesity might be related to OSA, it is much less commonly associated with the condition than is

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adult obesity. Left untreated, OSA can lead to further serious complications in children, including neurocognitive impairment and cardiovascular disease.[13] A parallel study of identical twins from 17 cases of nonobese children with OSA demonstrated differential growth and hormonal balance between OSA and non-OSA siblings despite the same genetic background.[10] However, there is controversy related to the development of pediatric OSA and impaired orofacial growth due to multifactorial disorders.

Repetitive episodes of oxygen desaturation during sleep underlie the pathology of pediatric OSA.[14] The ventilatory responses to these episodes are weaker in children than in adults with OSA.[15] Sustained hypoxia induces sternohyoid muscle maladaptation in growing rats, and brainstem hypoxia elicits selective upper but not lower respiratory muscle depression.[16] It is possible that OSA in young children can cause intermittent hypoxia (IH), which may lead to improper jaw development and worsening of respiratory function, although no research addressing these possibilities has been published. No reports have described the role of IH in the osteogenesis of the craniofacial skeleton in vivo, so the fundamental question is whether IH can induce craniofacial bone changes related to the development of the micromandible.

The growth spurt stage of the maxillofacial bones differs from that of the longitudinal bones and neural crest; boys undergo mandibular skeletal growth during adolescence.[17] In rats, the maxillofacial bones undergo striking growth and development from prepubertal to young adult periods.[18,19] In this study, we investigated the effects of IH on the dentofacial bones and tongues of prepubertal rats.[20] The experimental design attempted to isolate IH in pediatric OSA from other factors that might affect skeletal growth and bone metabolism (eg, dietary differences) to clarify the possible effects of the respiratory disturbance on skull growth.[21]

MATERIAL AND METHODS

The experimental procedures were performed according to the Guide for the Care and Use of Laboratory Animals published by the U.S. National Institutes of Health (NIH publication 85-23, revised 1996) under a protocol approved by the Institutional Animal Care and Use Committee of the University of Tokyo (P12-149). Seven-week-old male Sprague-Dawley rats were divided into 2 groups: the experimental group underwent IH at 20 cycles per hour (nadir, 4% oxygen; peak, 21% oxygen; 0% carbon dioxide) (IH group), and the normoxia (N) group was exposed to normoxic conditions (room air). The animals were housed in the same plastic cage placed next to the cage equipped with the IH apparatus for 8 hours per day during the 12-hour "lights on" period, as previously described.[20,22,23] The noise level for the N group was similar to that of the IH group in the adjacent cages to minimize noise stress-related differences. Moreover, the rats were pair fed to exclude dietary effects on growth. After 6 weeks, the rats were anesthetized with an intraperitoneal injection of sodium pentobarbital and killed by cervical dislocation.

Cephalometric analysis of the craniofacial skull was performed after the experimental period. Lateral and dorsoventral cephalometric radiographs were taken with a soft x-ray machine (CMB-2; SOFTEX, Tokyo, Japan) to evaluate craniofacial growth. The head position of each rat was fixed with a pair of ear rods.[19,23] The sagittal and transverse cephalometric radiograph settings were 50 kVp and 15 mA with 5-second impulses. Thirteen lateral and 6 dorsoventral landmarks were identified on the cephalometric radiographs to measure craniofacial growth by an author (Y.K.) (Fig 1, *A* and *B*): the most posterior and superior ends of the skull, the intersection between the frontal bone and floor of the anterior cranial fossa, the most anterior ends of the nasal bone, the most posterior and inferior ends of the occipital condyle, the most superior ends of the mandibular condyle, the most posterior ends of the mandibular ramus, the most concave portion of the inferior border of the mandibular corpus, the most inferior and anterior points of the lower border of the mandible, the most inferior and anterior points of the alveolar bone of the maxillary incisor, and the anterior and superior ends of the alveolar bone of the mandibular incisor. Cephalometric analysis of the dorsoventral radiograph was performed by evaluating the following points to quantify craniofacial growth (Fig 1, *B*): the posterior end of the palate on the midline, the points on the lateral portion of the zygomatic arch that pass the posterior end of the palate on the midline, the most anterior and medial points within the bilateral temporal fossae, the anterior end of the mandible on the concavity of the mandibular left and right incisors, and the posterior end of the mandibular body on the left and right. Each measurement was repeated and double-checked 3 times.

Fifteen linear distances between the cephalometric landmarks were measured using digital imaging software (Photoshop CS6 Extended; Adobe Systems, San Jose, Calif) as previously described.[23] Sagittal distances were measured for the total skull length, cranial vault length, and posterior neurocranium height in the neurocranium; nasal bone length and midface length in the viscerocranium; and total mandibular length from the condylar head to the mandibular incisor, total mandibular length from the condylar head to menton, ramus

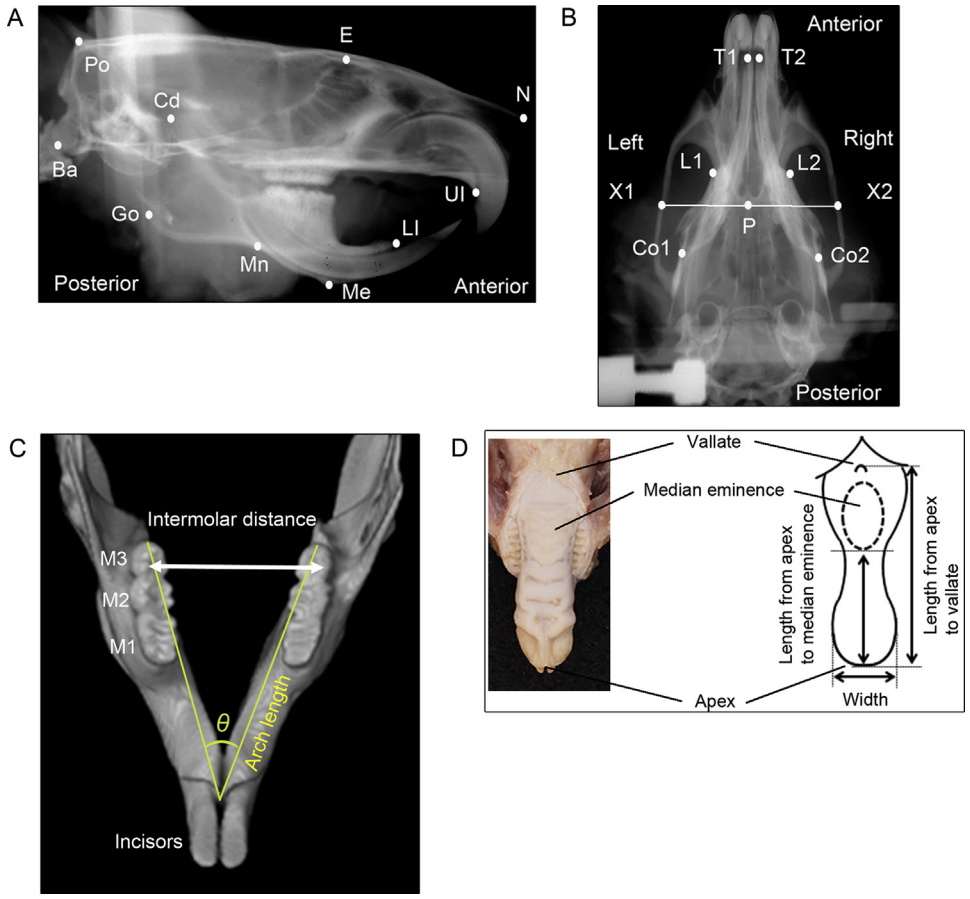

Fig 1. Analysis of rat dentofacial morphology. Locations of cephalometric landmark points on **A,** lateral, and **B,** dorsoventral cephalograms. **C,** Morphologic analysis of the rat dental arch; **D,** anatomic tongue measurement landmarks.

height from the condylar head to the inferior border of the mandibular corpus, total corpus length, posterior corpus length, and anterior corpus length in the mandible. Transverse distances on dorsoventral radiographs were measured for the bizygomatic width, palatal width, and mandibular body width.

After 6 weeks of IH, precise impressions of the mandibular and maxillary dental arches were acquired with rubber-based dental impression material (Exafine; GC, Tokyo, Japan) for measurements of dental arch width, length, and angle. The width and length of each dental arch were measured 3 times on a study model made of resin-fortified, low-expansion die stone (ResinRock; Whip Mix, Louisville, Ky) according to a previous report.[24] The intermolar distances between the outermost points on the buccal crown surfaces of the bilateral molars were measured with a sliding caliper (YS-32; YDM, Tokyo, Japan) to obtain the maxillary and mandibular dental arch widths (Fig 1, *C*). The dental arch length was measured as the distance from the lingual gingival margin between the bilateral central incisors to the distal ends of the bilateral third molars. The ratio of the maxillary to mandibular dental arch widths was calculated to check the discrepancy between the maxillary and mandibular transverse dental arches.

The maxilla and mandible were separately scanned with a phantom by microcomputed tomography (SMX-100CT; Shimadzu, Kyoto, Japan). The arch angle was measured on the appropriate cross section of the reconstructed computed tomography image using 3-dimensional image-analysis software (TRI/3-D-BON; Ratoc System Engineering, Tokyo, Japan) to assess differences in directional arch growth in the horizontal dimension (Fig 1, *C*).

To evaluate tongue dimensions, the distances between the apex and vallate and between the apex and median eminence of the tongue were measured using the sliding caliper according to the method of Reiner

Table I. Rats' body weight (grams) changes

	IH				*N*						
	Rats (n)	*Mean*	*SD*	*SE*	*Rats (n)*	*Mean*	*SD*	*SE*	*Mean difference*	P *value*	t *value*
Baseline	8	220.00	5.35	1.89	7	220.71	9.32	3.52	0.71	0.826	0.18
6 weeks	8	317.50	27.12	9.59	7	320.00	18.26	6.90	2.50	0.836	0.21

et al[25] (Fig 1, *D*). Tongue width was measured at the point where the anterior tongue began to curve to form the tongue tip. Tongue size was normalized to the mandibular width and length obtained from the dorsoventral cephalometric analysis.

Statistical analysis

An average of 6 rats per group was proposed in this study based on institutional animal ethics approval and the degree of impaired maxillofacial growth in young rats under IH reported by Kuma et al.[23] Two types of statistical methods were used to calculate appropriate sample size. A preliminary power analysis indicated that 8 rats would be necessary to show impaired maxillofacial growth with $\alpha = 0.05$ and 80% power. However, the resource equation method is the preferred method of determining sample size, particularly for animal studies.[26] Using this approach, the error difference should be between 10 and 20; the error difference value of this study was 10. Because the variances of growth data obtained in the groups were moderately small and well controlled by pair feeding, the statistical test results provided useful information for our evaluation. Body weights were expressed as means and standard deviations, and morphometric analysis data were expressed as medians and standard errors. Statistical calculations were performed using JMP software (version 10.0; SAS Institute, Cary, NC). We checked the normality and variance of the data using the Shapiro-Wilk normality test and the F test. The Welch *t* test was used for data with a normal distribution and unequal variance. Linear measurement-based data were compared using the Mann-Whitney U-test for nonparametric data. Differences were considered significant at $P < 0.05$.

RESULTS

The pair-fed rats were exposed to IH or N for 6 weeks, and there was no significant difference in body weight change between the 2 groups after the entire period (Table I). Lateral cephalometric images showed distoclusion of the first molar between the maxilla and mandible in the IH group (Fig 2, *A* and *B*). Growth retardation in the nasal bone length (−1.10 mm) was observed in the IH rats compared with the N rats (Table II). In the sagittal plane, there was no difference in the midfacial length between the IH and N groups. The total size of the mandible was significantly smaller in the IH group than in the N group ($P < 0.05$). In the mandible, the sagittal dimension of the ramus (−1.05 mm) and gonion (−0.54 mm) regions were significantly smaller in the IH group ($P < 0.05$) (Table II). However, there was no difference between the 2 groups in the anterior portion of the mandibular body (Table II).

On the dorsoventral cephalometric radiograph, the bigonial width between the 2 posterior ends of the mandibular body (−0.78 mm) was significantly smaller in the IH group ($P < 0.05$) (Table III). The bizygomatic width and palatal width were not different between the 2 groups.

Dental arch morphology was compared between the IH and N groups to evaluate the effects of IH on the dental arch growth in rats exposed to IH. The maxillary dental arch was narrower and more tapered, and the mandibular dental arch was shorter in the IH than in the N group (Table IV). Morphometric analysis of the dentition showed a significantly wider mandibular dental arch ($P < 0.05$) and a narrower maxillary arch in the IH group than in the N group (Table IV). The arch grew differently with respect to width and length, and the arch angle was significantly greater in the IH than in the N group in the mandible ($P < 0.05$), but not in the maxilla (Table IV). The ratio of the mandibular to the maxillary dental arches was significantly larger in the IH group ($P < 0.01$), demonstrating a distinct discrepancy between the maxilla and the mandible (Table V). However, the lengths of the mandibular arch were different between the IH and N groups.

Linear measurements of rat tongues were performed to calculate the proportional changes in tongue and dentofacial structures in the IH group. There were no differences in tongue width or length between the IH and N groups (Table VI). However, the dorsoventral cephalometric radiograph showed that the ratio of tongue width to mandibular width was significantly larger in the IH than in the N group (+4.2%; $P < 0.05$). Also in the IH group, the length of the tongue from the apex to the vallate papillae was enlarged relative to the length of the mandible compared with the N group (+3.5 %) (Table VI).

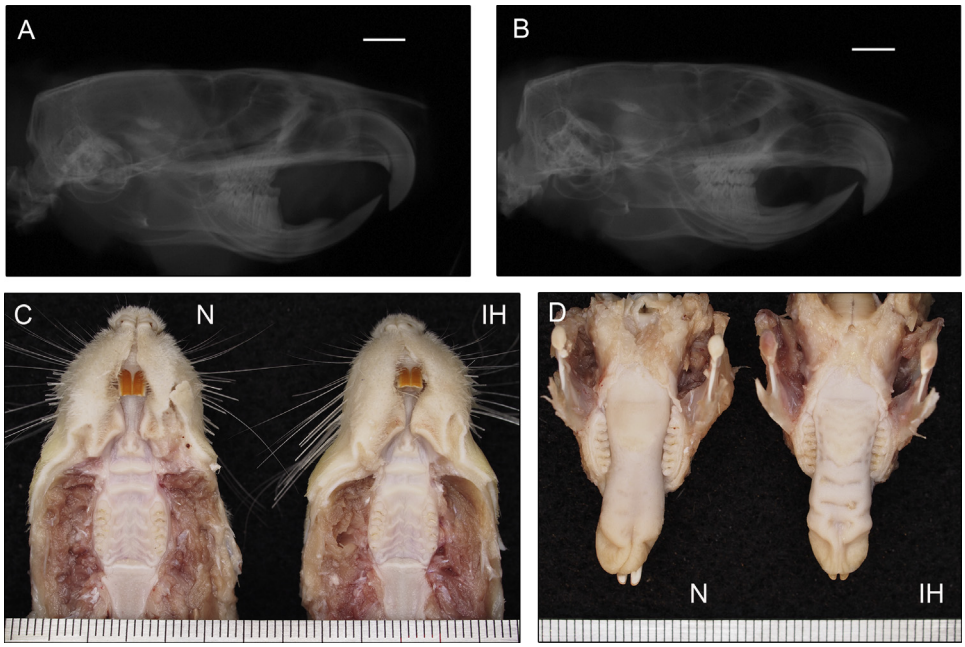

Fig 2. Imaging after 6 weeks of IH exposure: **A** and **B,** representative lateral radiographs from the N and IH groups, respectively; **C** and **D,** representative photographs of the dental arches in the maxilla and mandible, respectively.

Table II. Cephalometric assessment of craniofacial morphology in IH and N rats

	IH				*N*						
Variable	*Samples (n)*	*Mean*	*SD*	*SE*	*Samples (n)*	*Mean*	*SD*	*SE*	*Mean difference*	P *value*	t *value*
Neurocranium											
Po-N (mm)	6	50.56	0.63	0.26	5	51.63	0.67	0.30	1.07	0.083	2.72
Po-E (mm)	6	29.80	0.60	0.24	5	30.00	1.01	0.45	0.19	0.780	0.37
Po-Ba (mm)	6	11.11	0.23	0.09	5	11.22	0.33	0.15	0.10	0.315	0.60
Viscerocranium											
E-N (mm)	6	21.25	0.46	0.19	5	22.35	0.33	0.15	1.10	0.008†	4.62
Po-UI (mm)	6	46.65	0.72	0.29	5	47.18	0.62	0.28	0.52	0.235	1.29
Ba-UI (mm)	6	45.16	1.24	0.50	5	46.33	0.47	0.21	1.17	0.055	2.13
Mandible											
Cd-L1 (mm)	6	26.18	0.41	0.17	5	27.31	0.80	0.36	1.13	0.031*	2.86
Cd-Me (mm)	6	23.22	0.33	0.13	5	24.43	0.78	0.35	1.21	0.023*	3.23
Cd-Mn (mm)	6	16.25	0.53	0.22	5	17.30	0.65	0.29	1.05	0.045*	2.40
Go-Me (mm)	6	19.40	0.39	0.16	5	20.22	0.23	0.10	0.82	0.023*	4.34
Go-Mn (mm)	6	11.80	0.33	0.13	5	12.33	0.20	0.09	0.54	0.036*	3.35
Me-Mn (mm)	6	7.92	0.25	0.10	5	7.88	0.21	0.09	0.04	0.927	0.32

Linear measurements of the neurocranium, viscerocranium, and mandible on the lateral cephalograms were obtained from the IH and N rats after a 6-week experimental period.
Po-N, Total skull length; *Po-E*, cranial vault length; *Po-Ba*, posterior neurocranium height; *E-N*, nasal bone length; *Po-U1*, midface length from Po to U1; *Ba-U1*, midface length from Ba to U1; *Cd-L1*, total mandibular length from the condylar head to mandibular incisor; *Cd-Me*, total mandibular length from the condylar head to menton; *Cd-Mn*, ramus height; *Go-Me*, total corpus length; *Go-Mn*, posterior corpus length; *Me-Mn*, anterior corpus length.
*$P < 0.05$; †$P < 0.01$.

Table III. Cephalometric analysis of dorsoventral radiographs in IH and N rats

	IH				*N*						
Variable	*Samples (n)*	*Mean*	*SD*	*SE*	*Samples (n)*	*Mean*	*SD*	*SE*	*Mean difference*	P *value*	t *value*
Neurocranium											
X1-X2 (mm)	6	23.25	0.33	0.14	5	23.30	0.45	0.20	0.05	0.784	0.20
Viscerocranium											
L1-L2 (mm)	6	10.64	0.13	0.05	5	10.73	0.15	0.06	0.09	0.314	1.07
Mandible											
Co1-Co2 (mm)	6	13.35	0.62	0.25	5	14.13	0.46	0.21	0.78	0.036*	2.38

Linear measurements of the neurocranium, viscerocranium, and mandible on the dorsoventral cephalometric radiographs were obtained from IH and N rats after a 6-week experimental period.
X1-X2, Points on the lateral portion of the zygomatic arch that pass the posterior end of the palate on the midline; *L1-L2*, most anterior and medial points in the bilateral temporal fossae; *Co1-Co2*, posterior end of the mandibular body on the left and right.
*P <0.05.

Table IV. Rat dental arch morphology

	IH				*N*						
Variables	*Samples (n)*	*Mean*	*SD*	*SE*	*Samples (n)*	*Mean*	*SD*	*SE*	*Mean difference*	P *value*	t *value*
Intermolar arch width											
Maxilla											
M1 (mm)	6	9.13	0.35	0.14	5	9.48	0.11	0.05	0.36	0.079	2.32
M2 (mm)	6	9.20	0.26	0.11	5	9.50	0.11	0.05	9.20	0.044*	2.40
M3 (mm)	6	8.89	0.12	0.05	5	9.16	0.13	0.06	0.27	0.022*	3.59
Mandible											
M1 (mm)	6	8.81	0.28	0.12	5	8.28	0.15	0.07	0.53	0.027*	3.95
M2 (mm)	6	9.34	0.24	0.10	5	8.94	0.20	0.09	0.40	0.022*	3.03
M3 (mm)	6	9.65	0.29	0.12	5	9.17	0.34	0.15	0.48	0.067	2.50
Arch length											
Maxillary arch (mm)	12	21.47	0.13	0.04	10	21.89	0.20	0.06	0.42	0.0004†	5.78
Mandibular arch (mm)	12	16.95	0.62	0.18	10	16.89	0.13	0.04	0.06	0.335	0.30
Arch angle											
Maxillary arch (°)	6	21.90	0.46	0.19	5	22.76	1.06	0.48	0.87	0.143	1.69
Mandibular arch (°)	6	35.68	1.27	0.52	5	33.17	1.42	0.63	2.51	0.014*	3.06

Measurements of the intermolar arch width, arch length, and arch angle were made after a 6-week experimental period. Data of arch length were obtained from both the right and left sides of each rat.
M1, First molar; *M2*, second molar; *M3*, third molar.
*P <0.05; †P <0.01.

Table V. Size relationship between the mandibular and maxillary dental arches

	IH				*N*						
Variable	*Samples (n)*	*Mean*	*SD*	*SE*	*Samples (n)*	*Mean*	*SD*	*SE*	*Mean difference*	P *value*	t *value*
Relative mandibular arch width to the maxillary arch											
M1 (%)	6	96.59	3.07	1.25	5	87.35	1.58	0.70	9.24	0.008*	6.43
M2 (%)	6	101.58	2.72	1.11	5	94.10	1.66	0.74	7.48	0.008*	5.61
M3 (%)	6	108.52	2.64	1.08	5	100.11	3.29	1.47	8.42	0.008*	4.61

Data show the relative intermolar arch widths of the mandible to the maxilla after a 6-week experimental period.
M1, First molar; *M2*, second molar; *M3*, third molar.
*P <0.01.

Table VI. Tongue dimensions in IH and N rats

	IH				N						
Variable	*Samples (n)*	*Mean*	*SD*	*SE*	*Samples (n)*	*Mean*	*SD*	*SE*	*Mean difference*	P *value*	t *value*
Tongue width (mm)	6	7.87	0.46	0.19	5	7.73	0.34	0.15	0.14	0.587	0.56
Tongue length											
Apex to median eminence (mm)	6	14.64	0.92	0.37	5	14.80	0.38	0.17	0.16	0.644	0.38
Apex to vallate (mm)	6	24.61	0.88	0.36	5	24.94	0.59	0.26	0.33	0.762	0.74
Tongue width/Co1-Co2 (%)	6	58.93	2.71	1.11	5	54.72	2.09	0.94	4.21	0.018*	2.90
Tongue length/Go-Me											
Apex to median eminence (%)	6	75.42	3.54	1.44	5	73.22	2.58	1.15	2.20	0.132	1.19
Apex to vallate (%)	6	126.80	2.43	0.99	5	123.34	2.18	0.98	3.46	0.018*	2.48

Measurements of tongue dimensions were made after a 6-week experimental period. Tongue length was measured from apex to vallate and to median eminence. Relative tongue width and length were compared with the width of the mandibular body (*Co1-Co2*) and the length of the mandibular body (*Go-Me*).
*$P < 0.05$.

DISCUSSION

IH is the most pathognomonic factor associated with OSA and reportedly induces hypertension, pulmonary hypertension, and myocardial injury in rodents.[20,22] We demonstrated that IH induces the formation of a smaller mandible and a larger tongue in peripubertal rats as well as discrepant growth in the transverse dental arch.[18] Mandibular growth persists during adolescence, whereas maxillary growth peaks before puberty in rats, suggesting that IH induces earlier intramembranous ossification and growth delay in the mandibles of growing rats.[19]

Children with OSA exhibit a narrower maxillary arch, deeper palatal height, and shorter mandibular dental arch than do healthy children.[27] The anterior open bite and distoclusion associated with micrognathia are related to a higher apnea-hypopnea index in children.[28] In children with OSA who exhibit mandibular retrognathia, adenotonsillectomy partially normalizes the dentofacial morphology and dental occlusion, thereby reducing snoring.[29] These findings support the hypothesis that IH could at least partly induce craniofacial growth retardation and anatomic imbalance of the upper airway and tongue which are pathognomonic to OSA.[30] Male patients with OSA exhibit wider mandibular divergence, smaller mandibular internal length, and smaller area at the mandibular base plane, although obesity is only a minor factor in their population.[31] Common morphologic changes appear to be present in children and adults with OSA. Therefore, correction of the dentofacial morphologic changes in children with OSA could prevent, or at least mitigate, the development of adult OSA and its associated cardiovascular morbidities and potential for early mortality.[32]

Complications related to OSA pathology make it harder to identify the root causes of impaired craniofacial growth in children with OSA. Metabolic factors play significant roles in the mechanisms controlling the association of body weight and fat mass with bone mass.[33] In fact, body weight is a significant predictor of bone mass in growth.[21] We used several methods in the experimental design to control for as many of these complicating factors as possible. First, a pair-fed rodent model was used to control for body weight changes in the animal model. In this way, food intake and thus metabolic effects on bone growth were similar across the groups. Second, we used animals of the same strain (with shared genetic backgrounds) to control for the many genetic factors related to the pathogenesis and development of OSA.[20] In this study, IH did not affect body weight. In a previous study, IH failed to affect either the nasal bone length/tibial length ratio or the tibial length, suggesting that craniofacial development was specifically affected.[23]

In addition to a shorter mandible, IH induced a narrow maxillary dentition and an enlarged mandibular dentition in our study, resulting in a crossbite. Development of the dentition is affected by obstructive breathing to compensate for the upper airway narrowing in children with OSA exhibiting a micromandible. The apnea-hypopnea index is inversely correlated with the width of the maxillary dental arch in children aged 3 to 10 years.[28] Maxillary arch constriction is reportedly caused by mouth breathing, tongue and body posture during sleep in children with OSA, and snoring, although the role of maxillary constriction in the etiology of OSA is controversial.[2] Moreover, a narrower maxillary dentition, as reflected by a smaller ratio of the dental arch width to alveolar width, is also associated with the apnea-hypopnea index in adults with OSA.[34]

The rats in the IH group in this study had a larger tongue relative to the mandible. In adults with OSA, the mandibular dental arch enlarges as the tongue

increases in size, and the apnea-hypopnea index decreases.[35] However, there is little evidence of tongue enlargement in children or adults with OSA. The association of tongue size with IH and OSA severity in animals and humans requires further study.

Several orthopedic reports focusing on OSA have shown bony changes in adult patients with OSA[36] as well as mature animals exposed to IH.[37] IH induces osteogenic differentiation in mesenchymal stromal progenitor cells differently between the mandible and the tibia.[38] However, there have been no reports that focused on skeletal growth and bone metabolism in children with OSA. Further study is required to prove the hypothesis that IH attenuates craniofacial bone growth.

This study described the similarities in the morphologic changes of the craniofacial bones between rats exposed to IH and growing children with OSA but was limited in 2 particular ways. First, IH is the primary contributor to the pathogenesis of OSA, but our results cannot be directly applied to human OSA because of the craniofacial differences between humans and rodents. Second, OSA pathogenesis is complex and is affected by other confounding factors including age, sex, and metabolic factors that were not addressed here. Further study is needed to verify the effect of IH on bone metabolism in the growing human body, to allow for generalization of the role of IH seen here to children.

CONCLUSIONS

We confirmed the contribution of IH to the morphologic changes in murine craniofacial bones during relatively short periods corresponding to the prepubertal period. Our rat model demonstrated the ability of IH to impair jaw development.

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