The European Journal of Orthodontics Advance Access published August 17, 2005

European Journal of Orthodontics 1 of 7
doi:10.1093/ejo/cji028

Influence of growth hormone on the craniofacial complex of transgenic mice

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SUMMARY Growth hormone (GH) secretion affects bone and cartilage physiology. This study investigated the effect of GH on the size of the craniofacial structures and their angular relationship. Three different models of mice with a genetically altered GH axis were used: GH excess (giant), dwarf GH antagonist (dwarf-Ant), and dwarf GH receptor knockout (dwarf-KO) mice. Each model was compared with the corresponding wild type (Wt). Five craniofacial distances were analysed: craniofacial length, upper face height, mandibular anterior height, mandibular ramus length, and mandibular corpus length. In addition, upper and lower incisor lengths and four angular relationships, nasal bone with cranial base, maxillary plane with cranial base, mandibular plane with cranial base, and the angle of the mandible, were determined. Data were analysed by one-way ANOVA.

Craniofacial length, upper face height and mandibular corpus length were significantly increased in the giant mice and significantly reduced in the dwarf mice. Mandibular anterior height and mandibular ramus length were significantly affected in the dwarf-KO mice but not in the giant mice. The length of both the upper and lower incisors was significantly increased and reduced in the giant and dwarf-KO mice, respectively. In addition, the angle of the mandible was significantly increased in the giant mice and significantly reduced in the dwarf mice. It is concluded that GH plays a major role in the growth and development of the craniofacial complex by directly and indirectly modulating the size and the angular relationships of the craniofacial structures, including the incisor teeth.

Introduction

As its name indicates, the major action of growth hormone (GH) is the promotion of post-natal growth. In humans, hyposecretion of GH during development leads to dwarfism. Hypersecretion of this hormone from pituitary adenomas prior to closure of the growth plates during adolescence results in gigantism, whereas during adulthood it results in acromegaly (Stewart, 2000). Height normalization in GH-deficient children and in those born small for gestational age following long-term GH treatment (Van Pareren *et al.*, 2003) implies a direct impact of GH on bone mass and bone size (Shalet *et al.*, 2003). In the craniofacial complex, this hormone regulates cartilage formation (Pirinen, 1995). GH treatment accelerates craniofacial growth in children (van Erum *et al.*, 1997), and face height is altered by GH, particularly by influencing the height of the posterior face (Pirinen *et al.*, 1994). GH has also been proposed to affect the rotation of the mandible during craniofacial growth (Rongen-Westerlaken *et al.*, 1993). However, its effect on the size of craniofacial bones and how this action affects their relationships have not been studied.

During the last two decades, a number of lines of mice expressing different GH analogues have been developed (Kopchick *et al.*, 1999), allowing the use of animal models to understand the different features present in GH-related skeletal alterations. Available models are bovine GH excess transgenic (giant) mice, releasing GH excess (Kopchick *et al.*, 1999), dwarf GH antagonist excess (dwarf-Ant) mice (Chen *et al.*, 1991a), and GH receptor knockout (dwarf-KO) mice, with GH insensitivity (Hull and Harvey, 1999). These animal models help to identify the actions of GH on the target tissues, bone, cartilage and teeth, leading to insights into the roles of this hormone during growth and development.

GH produces its effect directly on tissues or indirectly through the synthesis of insulin-like growth factor-I (IGF-I) (Green *et al.*, 1985). It appears that in bone and teeth GH may produce its effect directly (Zhang *et al.*, 1992; Visnapuu *et al.*, 2001), whereas on cartilage, the effect is IGF-I dependent (Visnapuu *et al.*, 2001). As craniofacial structures develop from intramembranous and endochondral ossification, any alteration in GH production may affect them by direct or indirect action (GH/IGF-I axis). The purpose of this study was to investigate whether alterations in the GH/IGF-I axis in GH transgenic mice affect the size of the craniofacial bones, jaws and incisors. Additionally, the effect of alterations in the GH/IGF-I axis on the angular relationship between craniofacial bones with the cranial base as well as the angular relationship between the mandibular ramus and corpus were investigated.

Materials and methods

These experiments were carried out in accordance with the guidelines of the National Health and Medical Research Council of Australia. Ethical clearance for this study was obtained from the University of Queensland Animal Ethics Committee.

Forty-two mice from three different genetically altered groups were compared with their wild type (Wt) littermates. Litters of giant mice were obtained by crossing male giant mice carrying a bovine GH transgene with female Wt animals of the same strain (Kopchick *et al.*, 1999). The second group were dwarf mice obtained by crossing males carrying a bovine GH antagonist transgene in which lysine was substituted for glycine 119 (Chen *et al.*, 1991b) with female mice of the same strain (C57Bl/6J). This crossing delivered litters carrying the genetically dominant GH antagonist (dwarf-Ant). The third group, dwarf-KO, resulted by pairing heterozygous 129 OLA/BalbC males with heterozygous females from the same strain (Kopchick *et al.*, 1999). The genotypes of mouse pups were confirmed by polymerase chain reaction (PCR) immediately after birth using tail blood DNA.

Each group of genetically altered mice comprised three males and three females for each phenotype. In the dwarf-KO group, three heterozygous male and three heterozygous female were also included. The animals were maintained under identical dietary and lighting regimens and in specific pathogen-free conditions. All mice were sacrificed 45 days after birth and the heads were bisected sagitally at the midline and fixed in 4.0 per cent paraformaldehyde in phosphate-buffered saline for 24 hours at 4ºC. The right halves of the heads were X-rayed (Watson-Victor SF1 X-ray, Medic Corp., Wingate, Wellington, New Zealand) with the flat internal surface against the film. Radiographs (Kodak, ultra-speed DF50®, Rochester, New York, USA) with 1.25 seconds of exposure and 200 Kv were taken. A radio-opaque scale was placed on the radiographic film as a morphometric control.

The radiographic images were scanned using a Bio-Rad GS-700 imaging densitometer (Bio-Rad Laboratories, Hercules, California, USA) and the landmarks were determined on the computerized pictures. The measurements were made on screen images using pre-calibrated morphometric analyser software (Scion Image, Scion Corp., Frederick, Maryland, USA).

Longitudinal measurements

Five distances were measured to determine the differences in the size of the craniofacial bones for each genotype with its matching Wt (Figure 1A). Craniofacial length was determined by measuring the distance from the most anterior point of the nose (A) to the most posterior point of the cranium (Po). The height of the upper face was measured from the top of the suture between the nasal bone and the cranium (N) to the point where the crown of the first upper molar tooth touches the maxillary bone (Mu). Mandibular anterior height was measured from the tip of the mesial cusp of the first lower molar tooth (Ml) to the most antero-inferior point at the lower border of the mandible (Pg). Mandibular ramus and corpus lengths were measured separately. The length of the mandibular ramus was determined by measuring the distance between the most postero-superior point of the mandibular condyle (Co) and the most postero-inferior point of the lower border of the mandible (Go). The distance between Go and Pg determined the length of the mandibular corpus.

The length of the incisors was determined by measuring the external or buccal surface of the incisor from the incisal edge (Iu1 or Il1) to the developmental tip (Iu2 or Il2) of both maxillary and mandibular incisors (Figure 1A).

Angular measurements

The relationships of the cranial base with the nasal bone, the maxilla and the mandible in the three different groups of mice were determined by three different angles (Figure 1b). The plane of the cranial base was determined from point N to the most inferior point of the occipital bone (Ba). Thus, the angle formed between the plane of the cranial base and the plane A–N was used to determine the relationship between the nasal bone and the cranial base (AN/NBa). The angle formed by the plane of the cranial base with that from

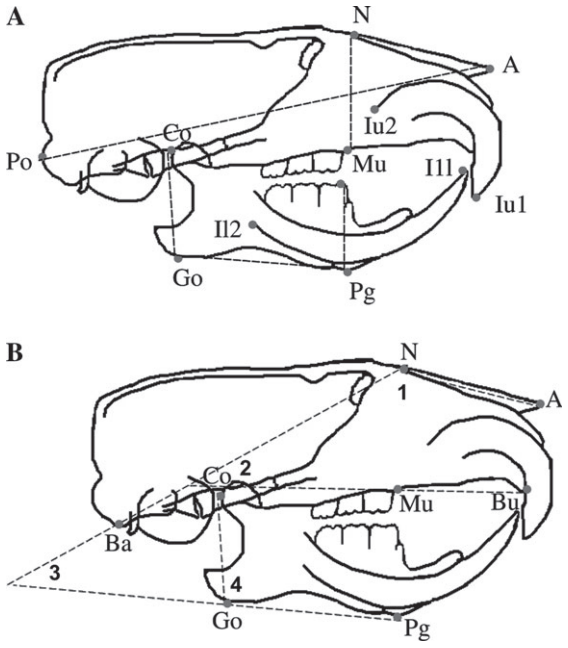

Figure 1 (A) Landmarks and longitudinal measurements used to determine the size of the craniofacial structures and the length of the incisors in the growth hormone genetically modified mice. (B) Angular relationships between the craniofacial structures. (1) Nasal bone and cranial base; (2) maxilla and cranial base; (3) mandibular corpus and cranial base; (4) mandibular corpus and ramus.

Mu to that point where the lingual aspect of the upper incisor touched the palate (Bu), was used to observe the relationship of the maxilla with the cranial base (BuMu/NBa). The angle formed by the plane from Go to Pg with the plane of the cranial base was measured to determine the relationship between the mandible and the cranial base (GoPg/NBa). AN/NBa was measured at the antero-inferior quadrant formed by the two planes. BuMu/NBa and GoPg/NBa were measured at the antero-superior quadrant formed by the planes. In addition, the relationship between mandibular corpus and ramus was determined by measuring the angle formed by the planes Co–Go and Go–Pg (CoGo/GoPg). The measured angle was that at the antero-superior quadrant formed by the planes (Figure 1B).

Statistical analysis

The angle N–Ba/Go–Pg was the only measurement considered to be biased by mouth opening. Therefore, only those radiographs with a Mu–Ml distance between 1.0 and 1.5 mm were used for the study. All measurements were performed three times by the same operator (GOR-Y). A very high intra-examiner agreement was determined by Spearman's test ($r > 0.98$). A final average from the different measurements was statistically analysed by one-way ANOVA. A Newman–Keuls post-test was performed when a significant difference at the 95 per cent level of confidence was observed. $P < 0.05$ was considered significant. The statistical analysis was performed using Prism 2.1 software (GraphPad Prism Software Inc., San Diego, California, USA).

Results

Some measurements yielded a significant difference when the data were analysed regarding gender within the three different groups. Therefore, the data were analysed independently for males and females within each group. The distances were calculated in millimetres and angular measurements were expressed in degrees. The mean values for each measurement in the three GH analogues and their corresponding Wt are reported in Table 1.

Longitudinal measurements

The giant mice showed a significant increase in craniofacial length (A–Po), upper face height (N–Mu), and mandibular corpus length (Go–Pg) when compared with their corresponding Wt. Conversely, these distances were significantly reduced in the dwarf-Ant and dwarf-KO mice. In the giant mice, mandibular anterior height (Ml–Pg) and mandibular ramus length (Co–Go) showed a tendency to increase, but they did not reach a significant difference. However, Ml–Pg and Co–Go were significantly reduced in the dwarf-KO mice and in the males from the dwarf-Ant group.

When the lengths of both maxillary and mandibular incisors were statistically analysed, a significant increase was observed for those teeth in the giant mice compared with their similar background strain controls. An opposite result was observed in the dwarf-KO animals where the length of the incisors was significantly smaller compared with their Wt matches. This significant reduction in the length of the incisors was also observed in the dwarf-Ant mice, but only in males. Even though a slight reduction was noted in the dwarf-Ant females, it did not reach significance. The longitudinal measurements as well as the lengths of both the upper and lower incisors were not significantly different when the heterozygous animals were compared with their Wt in the dwarf-KO group.

Angular measurements

Only two of the four angles measured demonstrated a significant difference. The A–N/N–Ba angle was significantly reduced in the dwarf-Ant and dwarf-KO mice compared with their corresponding Wt. Another angle showing a significant difference was the angle of the mandible (Co–Go/Go–Pg). This angle was significantly increased in the giant mice compared with their Wt. Conversely, there was a significant reduction in the Co–Go/Go–Pg angle when the dwarf-Ant and the dwarf-KO animals were compared with their matched Wt strain control.

Regarding the relationship of the cranial base with the maxilla and mandible, no significant differences were found when the different groups of genetically altered animals were compared with their corresponding Wt. In addition, no significant differences were found in those heterozygous mice compared with the similar genetic matches when the four measured angles were statistically analysed.

Discussion

Genetic and functional control of craniofacial growth is a complex process. Various parts of the skeleton have different modes of bone growth. It is also known that the effect of GH is different in the regions of the skull. The present study used three distinct groups of GH genetically altered mice to understand the action of GH on the craniofacial complex. The data show that GH modulates not only the size of the craniofacial bones, but also of the incisors. Additionally, the data also show that the angular relationships between some craniofacial structures are modulated by GH. It is well known that in humans (Forsberg *et al.*, 2002) as well as in animals (Young *et al.*, 1993; Bravenboer *et al.*, 1997; Li *et al.*, 2001; Forsberg *et al.*, 2002; Ramirez-Yañez *et al.*, 2004b) that GH affects the mineralized tissues within the craniofacial structures. Nevertheless, this is possibly the first study in animals correlating how a different GH status modifies the size of the craniofacial structures, and how their relationships may be affected by these changes.

Table 1 Longitudinal and angular measurements of the different structures in the craniofacial complex associated with the different growth hormone (GH) genetically modified mice. Significant increases were observed in craniofacial length (A–Po), upper face height (N–Mu), and length of the mandibular corpus (Go–Pg) in the GH excess mice (giant). The GH antagonist mice (dwarf-Ant) and the GH receptor disrupted mice (dwarf-KO) showed significant reductions in the same distances. Lower face (Ml–Pg) and mandibular ramus heights (Co–Go) were only significantly reduced in the dwarf-KO mice. A significant decrease in length was observed in the dwarf-KO group for both upper and lower incisors, whereas the giant mice showed a significant increase. The mandibular angle was significantly increased in the giant mice and significantly decreased in the dwarf mice (Ant and KO). Statistically significant differences with the corresponding wild type (Wt) Means and standard deviations (SD) are shown.

	Wt		Giant		Wt		Dwarf-Ant		Wt		Het		Dwarf-KO	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Longitudinal (mm)														
A–Po														
Male	27.23	± 0.99	30.84	± 0.59*	22.98	± 0.15	19.48	± 0.88*	22.98	± 0.59	22.78	± 0.69	19.76	± 0.63*
Female	23.05	± 0.41	24.25	± 0.21*	24.13	± 0.85	20.86	± 1.97*	22.57	± 0.95	22.36	± 1.02	19.55	± 0.81*
N–Mu														
Male	7.34	± 0.15	8.02	± 0.27*	5.86	± 0.27	4.81	± 0.15*	5.35	± 0.1	5.35	± 0.18	4.77	± 0.42*
Female	6.03	± 0.33	6.55	± 0.12*	6.03	± 0.26	5.18	± 0.61*	5.62	± 0.23	5.42	± 0.21	4.97	± 0.11*
Ml–Pg														
Male	4.59	± 0.15	4.66	± 0.05	3.67	± 0.15	3.15	± 0.06	3.43	± 0.15	3.32	± 0.06	2.71	± 0.05*
Female	3.39	± 0.21	3.49	± 0.21	4.08	± 0.66	3.46	± 0.39	3.49	± 0.35	3.43	± 0.31	2.77	± 0.21*
Co–Go														
Male	4.47	± 0.27	4.56	± 0.36	3.91	± 0.21	2.64	± 0.05*	3.46	± 0.33	3.43	± 0.16	2.85	± 0.06*
Female	3.71	± 0.36	3.77	± 0.23	3.6	± 0.37	3.33	± 0.79	3.7	± 0.41	3.66	± 0.06	2.91	± 0.16*
Go–Pg														
Male	11.32	± 0.27	11.87	± 0.21*	8.6	± 0.48	6.72	± 0.47*	8.47	± 0.24	7.92	± 0.11	7.03	± 0.26*
Female	9.05	± 0.17	8.61	± 0.05*	8.94	± 0.33	7.89	± 0.07*	8.62	± 0.46	8.47	± 0.24	6.78	± 0.42*
Upper incisor														
Male	11.01	± 0.1	11.9	± 0.41*	8.87	± 0.17	6.75	± 0.6*	8.95	± 0.51	8.61	± 0.31	5.9	± 0.42*
Female	7.99	± 0.33	8.71	± 0.3*	9.15	± 0.8	8.26	± 1.48	7.78	± 0.87	7.51	± 0.98	6.34	± 0.11*
Lower incisor														
Male	16.12	± 0.29	16.88	± 0.2*	11.52	± 0.11	9.47	± 0.18*	11.45	± 0.12	11.42	± 1.07	9.29	± 0.68*
Female	11.97	± 0.26	12.73	± 0.21*	12.79	± 0.8	11.32	± 1.52*	12.04	± 0.37	11.8	± 0.12	9.74	± 0.21*
Angular (degrees)														
AN/NBa														
Male	129.4	± 2.08	131.3	± 2.36	131.1	± 2.03	125.5	± 2.06*	132.2	± 0.96	129.7	± 1.67	126	± 2.37*
Female	129.2	± 2.19	125.3	± 1.87	129.9	± 2.04	126.2	± 1.1*	132.5	± 1.03	131.9	± 0.85	127.4	± 1.9*
BuMu/NBa														
Male	36.04	± 2.44	34.17	± 1.24	33.94	± 1.78	35.84	± 2.27	34.27	± 2.04	36.07	± 1.19	33.77	± 2.41
Female	32.7	± 0.95	32.84	± 0.82	37.69	± 1.63	35.68	± 1.92	33.24	± 2.22	30.36	± 2.5	32.33	± 2.34
GoPg/NBa														
Male	38.88	± 2.15	39.35	± 1.19	37.04	± 1.53	39.68	± 1.53	38.47	± 2.33	41.79	± 2.41	36.72	± 2.4
Female	33.71	± 0.86	36.18	± 2.16	40.4	± 2.22	39.51	± 1.32	37.6	± 2.23	35.63	± 2.12	39.25	± 0.08
CoGo/GoPg														
Male	101.3	± 2.05	106.8	± 2.18*	104.8	± 2.45	97.79	± 2.47*	96.92	± 2.43	100.3	± 2.28	91.72	± 1.5*
Female	93.84	± 2.43	105.3	± 2.47*	105.6	± 2.09	97.09	± 2.46*	98.85	± 2.16	97.7	± 1.07	93.63	± 1.85*

$P < 0.05$.

In giant mice, the increase in the length of the maxillary incisors may result in greater dimensions of craniofacial length and upper face height. Concomitantly, increases in the length of the mandibular incisors are accompanied by an increase in the length of the supporting mandibular corpus. Significant decreases in the length of both the maxillary and mandibular incisors were observed in the dwarf-KO animals. The dwarf-Ant mice showed a significant reduction in incisor length only in males, even though a slight but not significant reduction was noted in females. Reductions in incisor length are accompanied by reductions in craniofacial length, upper face height and the supporting mandibular corpus. The smaller maxillary incisors in the dwarf mice may also have an impact on the aperture of the AN/NBa angle, which was significantly reduced in those animals. In humans, patients with GH deficiency show a reduced maxillary and mandibular length (Pirinen *et al.*, 1994), and an association between decreased maxillary jaw size and maxillary tooth agenesis

has been reported (Tavajohi-Kermani *et al.*, 2002). Furthermore, disturbances in dental development caused by radiation therapy are associated with a significant reduction in craniofacial dimensions in children treated for malignant diseases (Dahllöf *et al.*, 1991). The current data and those findings in humans confirm that a link exists between the size of the teeth and the observed changes in the size of the supporting craniofacial structures. Thus, it may be hypothesized that the size of the teeth would be directly modulated by GH, and that the architectural support is also modulated by GH but in accordance with the size of the teeth. This suggestion does not deny a direct effect of GH on bone tissues, as craniofacial length was directly affected by the variations in the different GH analogues. However, a link between the inter-functional structures, in this case jaws and teeth, is suggested with a direct and indirect effect of GH on these structures.

The length of the mandibular ramus (Co–Go) increased in the giant mice, accompanied by a significant increase in the length of the incisors, both of them directly related to a significant opening of the mandibular angle (Co–Go/Go–Pg). In the dwarf-KO and dwarf-Ant mice, opposite results led to a closed angle of the mandible. In theory, these changes must also influence the aperture of the Go–Pg/N–Ba angle caused by a diagonal displacement of the Go–Pg plane in a downward (opened angle of the mandible) or upward (closed angle of the mandible) direction. However, this does not occur. The angular relationships between the maxillary and mandibular planes with respect to the cranial base did not vary significantly in any of the three different GH analogues when compared with their corresponding Wt littermates. The maintenance of a constant relationship of the maxillary and mandibular planes with the cranial base is important for a correct oral function with involvement of the complete dentition. This suggests that a compensatory mechanism occurs at the teeth, compensating for the changes in the surrounding structures, and so, maintaining a steady relationship between the planes of the mandibular corpus (Go–Pg) and the cranial base (N–Ba). Dental cementum biological activity is necessary for keeping the tooth in its correct position (Bosshardt and Schroeder, 1996; Newman, 1999). A direct relationship between GH status and the amount of cellular cementum has been reported (Smid *et al.*, 2004). Depending on the GH status, molar eruption may be stimulated or reduced to compensate the aperture of the angle of the mandible with no variation in the Go–Pg/N–Ba angle. Thus, it may be proposed that the angular relationships between the maxillary and the mandibular plane with the cranial base are maintained regardless of GH status, probably through the action of GH on the dental tissues of the molar teeth. However, the current results are not conclusive.

The length of the mandibular corpus was significantly increased in the giant mice, whereas in the dwarf-KO and dwarf-Ant animals it was significantly reduced. At the same time, the angle of the mandible was significantly affected by the GH status of the animals. This angle was significantly increased in the giant mice and significantly reduced in the dwarf-KO and dwarf-Ant animals. GH receptors are present on the mineralized tissues (Zhang *et al.*, 1992; Visnapuu *et al.*, 2001) and, thus, a direct action of GH is expected on intramembranous ossification. Therefore, the direct relationship observed in this study between the length of the mandibular corpus and GH status may be considered a direct action of GH on the bone tissues, and at the same time, an architectural adaptation to the size of the teeth, as proposed previously. In addition, the observed relationship between the mandibular angle and GH status supports the theory that the angle of the mandible adjusts itself during the growing process as a compensatory mechanism for those changes occurring at the craniofacial structures (Stutzmann and Petrovic, 1979). This agrees with observations in humans, where GH treatment initially produced a posterior rotation of the mandible, which later became anterior (Rongen-Westerlaken *et al.*, 1993). This may be an adaptive process to the correction of craniofacial deficits produced by GH treatment (Segal *et al.*, 2004).

In humans, a lack of GH seems to affect the vertical dimensions, particularly posterior face height (Pirinen *et al.*, 1994), which is basically determined by the length of the mandibular ramus. Anterior face height is determined by the upper and lower face heights. In the present animal study, these dimensions were reproduced by measuring the length of the mandibular ramus (posterior face height), the distance between N and Mu (upper face height), and the distance between Ml and Pg (lower face height). The current results show that not only the length of the mandibular ramus, but also the upper face, is significantly reduced in those mice with an attenuated action of GH. This may result either from decreased GH action on the chondral growth process in the mandibular condyles and in the nasal bone (Dahllöf *et al.*, 1991; Petrovic, 1994; Ramirez-Yañez *et al.*, 2004b), from a reduction in the size of the incisors, from less cellular cementum at the tips of the molar roots (Smid *et al.*, 2004), or a combination of these. Accordingly, the N–Mu and Co–Go distances were slightly increased in the giant mice. The animals in this experiment were sacrificed at 45 days of age when the mice were considered sexually mature but had not reached their final craniofacial size. Therefore, a lack of GH may have a direct impact on the upper face and length of the mandibular ramus at early stages of craniofacial development, whereas an excess of GH may affect face heights at this experimental stage, but its effect may become more significant later. These suggestions agree with those long-term monitored clinical findings where face height is reduced in short-stature patients (Midtbø *et al.*, 1996; Kjellberg *et al.*, 2000) and increased in acromegalic patients and in those treated with GH (Takakura and Kuroda, 1998; Simmons, 1999; Stewart, 2000).

In the giant mice, no significant increases were found in mandibular ramus length, whereas it was significantly reduced in the dwarf-KO animals and dwarf-Ant males, with a non-significant reduction observed in the dwarf-Ant females. The length of the mandibular ramus is mainly determined by the mandibular condylar cartilage, and the action of GH on this cartilage appears to be IGF-I dependent (Visnapuu *et al.*, 2001). A lack of GH accelerates cartilage cell maturation while mitotic activity is decreased, whereas an excess of GH increases mitotic activity but delays cartilage cell maturation (Ramirez-Yañez *et al.*, 2004b). It appears that blocking the mechanisms of action of GH on the mandibular condylar cartilage has a rapid impact on this cartilage, probably due to a reduction in IGF-I synthesis. In the mandibular condylar cartilage, a reduction in the number of cells available to mature, due to decreased mitotic activity, is associated with an accelerated maturation rate, which leads to less endochondral ossification (Ramirez-Yañez *et al.*, 2004a, b). Conversely, an excess of GH stimulates the mitotic activity of the cartilage, but after stimulating IGF-I synthesis (Visnapuu *et al.*, 2001). This is a more elaborate process that is associated with delayed cell maturation. Thus, higher rates of endochondral ossification are expected to be associated with GH excess, but, as suggested above, more time would be required to observe a significant increase in the length of the ramus.

Conclusions

The results of this study show that the size of the craniofacial structures and their angular relationships are directly linked to GH status. Differences were particularly found in the length of both maxillary and mandibular incisors, in the size of the craniofacial bones and in the length of the mandibular corpus and ramus between the three GH genetically modified mice studied. Furthermore, GH had an early effect on the vertical dimensions of the skull when GH was absent or reduced post-natally. The aperture of the angle of the mandible was affected by the changes in the size of the craniofacial structures, but the relationships between the maxillary and mandibular planes with the cranial base were maintained.

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Acknowledgements

This study was supported in part by a National Health and Medical Research Council of Australia Project Grant to Michael J. Waters, and by an Australian Dental Research Foundation Grant to William G. Young and Joseph R. Smid. The authors would like to thank John Kopchick and Karen Coschigano, Edison Biotechnology Institute and Department of Biomedical Sciences, Ohio University, Athens, OH, USA, for providing the genetically altered mice, and Jennifer Rowland, School of Biomedical Sciences, University of Queensland for genotyping the mouse pups.

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