The anatomy and embryology of the hypothalamus in relation to hypothalamic hamartomas

Jeremy L. Freeman

Children's Epilepsy Program, Department of Neurology and Murdoch Childrens Research Institute, Royal Children's Hospital, Parkville, Victoria, Australia; Department of Paediatrics, University of Melbourne, Victoria, Australia; and Epilepsy Research Institute, Austin and Repatriation Medical Centre, Heidelberg, Victoria, Australia

ABSTRACT – The hypothalamus is involved in a variety of autonomic, endocrine, neurological and behavioural functions including temperature, osmostatic and autonomic nervous system regulation, pituitary, thyroid, adrenal and gonadal control, thirst, appetite and weight control, memory and emotional behaviour including aggression and laughter, and biological (circadian) rhythms. The functional anatomy of the hypothalamus and its major afferent and efferent neurological connections are described, with particular reference to hypothalamic hamartomas (HH), gelastic seizures, MRI of the hypothalamus, and potential effects of surgery for HH. Normal development of the hypothalamus is reviewed in relation to models of forebrain development, descriptive hypothalamic embryology and the importance of known transcription factors. Potential environmental antecedents to HH development are discussed, and the significance for sporadic, isolated HH of several syndromes associated with HH is explored.

KEY WORDS: embryology, hypothalamic hamartoma, hypothalamus, neuroanatomy, neuroradiology

Correspondence:
Dr Jeremy L. Freeman
Department of Neurology
Royal Children's Hospital
Flemington Road, Parkville, VIC 3052
Australia
Tel: + 613 9345 5641
Fax: + 613 9345 5977
E-mail: jeremy.freeman@rch.org.au

Hypothalamic hamartomas (HH) are developmental malformations associated with a range of neurological and endocrine problems including intractable seizures, cognitive impairment, pervasive developmental disorders, behavioural disturbances and psychiatric disorders, and central precocious puberty [1-5]. This review will firstly present an outline of the structure and function of the hypothalamus in relation to HH, in consideration of the clinical features of the syndrome, and of the potential complications arising from its surgical treatment. Discussion of the endocrine hypothalamus, central nervous system control of appetite and weight, and endocrine aspects of surgery for HH is presented elsewhere in this issue (Freeman JL *et al.*).

The cause of sporadic HH is unknown; clues to the aetiology may be found in literature concerning the normal embryology of the hypothalamus, environmental causes of brain malformation and multiple congenital anomaly syndromes associated with HH. These subjects will also be reviewed briefly and avenues for further investigation discussed.

Neuroanatomy of the hypothalamus and hamartomas

Topography and divisions of the hypothalamus

In midsagittal section, the human hypothalamus is bound anteriorly by the *lamina terminalis*, posteriorly by a plane drawn between the posterior commissure and the caudal limit of the mammillary body, and superiorly by the hypothalamic sulcus. Ventrally, the hypothalamus encompasses the floor of the third ventricle, the inferior surface of which presents to the subarachnoid space below and is termed the *tuber cinereum* (grey swelling). The lateral boundaries include the internal capsule, cerebral peduncle and subthalamus on each side. Far from being sharply delimited however, the hypothalamus is broadly continuous with surrounding grey matter, the transition between structures often gradual, and in some places arbitrarily defined [6].

Based on the comparative hypothalamic anatomy of submammalian vertebrates, the hypothalamus can be divided into two longitudinal zones. In such animals, there is a cell-rich, medial zone flanked by an almost acellular lateral zone [6]. Although the cellularity of the lateral hypothalamic zone in higher vertebrates is greatly increased, the medial zone in humans contains the majority of named hypothalamic nuclei and can be roughly separated from the lateral zone by a sagittal plane passing through the anterior pillar of the fornix [7]. Some would further divide the medial zone into a thin periventricular zone and the adjacent medial zone, however the distinction in humans is not clear [6].

The hypothalamus is also commonly divided into regions along its anterioposterior axis *(figure 1)*. Rostral to the optic chiasm and extending dorsally to the anterior commissure and its bed nucleus is the preoptic region [8]. The supraoptic region lies above the optic chiasm. The tuberal region lies above and includes the *tuber cinereum*. The mammillary region includes the mammillary bodies and the posterior hypothalamic nuclei. One accepted definition of the boundary between the tuberal and mammillary regions is a plane extending along the caudal border of the column of the fornix [6]. The supraoptic and tuberal regions contain many nuclei embedded in myelin-poor hypothalamic grey matter, in sharp contrast to the mammillary region which is rich in myelin [9].

Hypothalamic nuclei and fibre connections

The hypothalamic nuclei were traditionally defined according to a combination of embryological, comparative anatomical and cytoarchitectonic criteria [9, 10]. Their organisation and connections have been studied more recently in laboratory animals using a combination of retrograde tracing experiments and immunohistochemical techniques [11]. These studies have shed new light on the variety of specific functions that have been attributed to
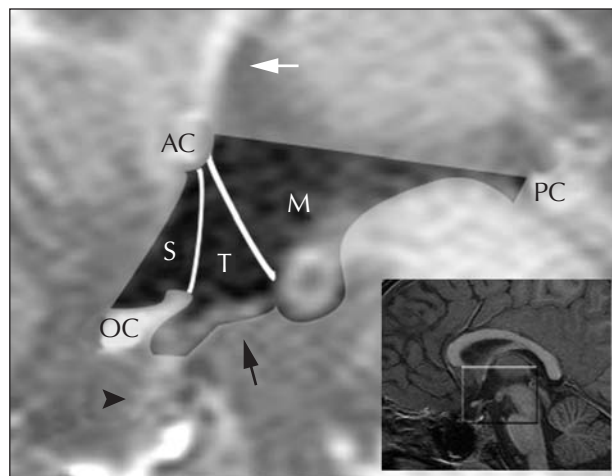

Figure 1. Mid-sagittal T1-weighted magnetic resonance image showing the outline of the normal hypothalamus (shaded area), anatomical landmarks defining the boundaries of the hypothalamus and the arrangement of regions within the hypothalamus.
Labelled are: **(AC)** *anterior commissure;* **(PC)** *posterior commissure;* **(OC)** *optic chiasm;* **(S)** *supraoptic (and preoptic) region;* **(T)** *tuberal region; and* **(M)** *mammillary region of the hypothalamus. Arrows indicate the position of the tuber cinereum (black arrow), the pituitary stalk (black arrowhead) and the anterior column of the fornix (white arrow). The inset shows the hypothalamus and surrounding brain at lower magnification.*

hypothalamic nuclei and cell types [12, 13]. A summary of the major nuclei, their location with respect to the described zones and regions, and their known or suspected functions is presented in *table 1*.

The hypothalamus receives inputs from a widely distributed network of fibres arising in the forebrain, brainstem and spinal cord. These connections usually have reciprocal efferent components and multiple intrahypothalamic destinations. For a more detailed account than can be given here, the reader is referred to Nauta and Haymaker [6], and to Saper [13]. The medial forebrain bundle traverses the lateral hypothalamus, is continuous with the septal area rostrally and with the brainstem tegmentum caudally, and has interstitial nuclei along its length. The dorsal longitudinal fasciculus connects nuclei of the periventricular medial zone with the periaqueductal grey. The amygdala has two main projections to the hypothalamus, the *stria terminalis* and the ventral amygdalofugal pathway. Input from the hippocampal formation is primarily through the *fornix*, the large postcommissural myelinated columns of which traverse the tuberal region, giving considerable input to nuclei of the medial zone before terminating in the mammillary body [6]. Other notable inputs include those from the retina, the circumventricular organs, basal frontal cortex and insula. The outputs of the mammillary body are among the most conspicuous efferent hypothalamic pathways, and are abundantly myelinated. The mammillary output divides close to its origin into the ascending mammillothalamic tract and the de-

Table 1. Major hypothalamic nuclei, their location and function

Region	Zone	Nucleus (n.)	Functional characteristics
Preoptic	Medial	OVLT	Osmoreception and chemoreception
		Subforniceal organ	Sensitive to circulating angiotensin, thirst centre
		Medial preoptic n.	Heat dissipation
		Intermediate n.	Sexually dimorphic nucleus
Supraoptic	Medial	Anterior n.	Heat dissipation; parasympathetic excitation
		Suprachiasmatic n.	Biological clock, circadian rhythms
		Paraventricular n.	Antidiuretic hormone (ADH), oxytocin secretion
	Both	Supraoptic n.	ADH, oxytocin secretion; osmoreception
Tuberal	Medial	Ventromedial n.	Satiety centre; aggression produced if destroyed
		Dorsomedial n.	Not well defined (structurally or functionally)
		Periventricular zone	Anterior pituitary (AP) control
		Infundibular (arcuate) n.	AP control; weight and appetite regulation
	Both	Tuberomammillary n.	Arousal, wakefulness
	Lateral	Lateral tuberal nuclei	Striking appearance, but unknown function
		Lateral hypothalamic area	Hunger centre
Mammillary	Medial	Mammillary body	Short-term memory; emotional experience?
		Posterior n.	Heat conservation; sympathetic excitation
All 3	Lateral	Lateral hypothalamic area	Interstitial nuclei of the medial forebrain bundle

OVLT = organum vasculosum of the lamina terminalis.

scending mammillotegmental tract. The mammillothalamic tract projects to the anterior nucleus of the thalamus, which in turn projects to the cingulate gyrus. The major endocrine outputs of the hypothalamus and their role in controlling pituitary function are discussed elsewhere in this issue (Freeman JL *et al.*).

Functional aspects

A large body of literature on hypothalamic function has collected over the last century, with data derived predominantly from animal experimentation and rarely from clinical observations. Studies initially involved either destructive lesioning or stimulation (chemical or electrical) of hypothalamic regions. The accuracy of spatial localisation was limited by the available technology. Despite these limitations, evidence accumulated that the hypothalamus is concerned with a broad range of endocrine, autonomic and neurological functions, integrated by virtue of the extensive network of reciprocal connections as described above. Apart from structures crossing the midline in the floor of the third ventricle, each of the hypothalamic nuclei and fibre connections are paired entities and, with the possible exception of the fornix (see below), no left-right differences or dominances have been noted in humans, although in animals, functionally significant lateral asymmetries are suspected [14].

The suprachiasmatic nucleus receives input from the retina directly as well as from the lateral geniculate nucleus, and exerts influence over pineal melatonin production. It is considered to be a biological clock with intrinsic pacemaker-like properties controlling, circadian rhythms of hormonal and behavioural function, entrained to the day-night cycle by its afferent connections [15].

The tuberomammillary nucleus extends through the posterior tuberal and anterior mammillary regions, in close association with the fornix and the mammillary body, and surrounding the distinctive lateral tuberal nuclei [9]. It contains the only histaminergic neurones in the brain. These project widely to the cerebral cortex bilaterally and to the spinal cord, and are important in maintaining a wakeful state, exemplified by the sedating effect of centrally acting antihistamines [13].

Sympathetic and parasympathetic outflow are regulated at the hypothalamic level. Although the areas involved overlap considerably, those associated with parasympathetic responses tend to be located rostrally, and those associated with sympathetic responses tend to be located caudally [16]. Temperature regulation is one example of the complementary roles played by the rostral and caudal hypothalamus in homeostasis. Stimulation of the rostral hypothalamus results in hypothermia, whereas destruction of this area causes an inability to dissipate heat in a warm environment; therefore, the rostral hypothalamus is regarded as a "heat loss" centre. In contrast, the caudal hypothalamus produces shivering, peripheral vasoconstricton and piloerection resulting in heat retention. Ther-

mosensitive neurons providing regulatory feedback are located in the preoptic region, whereas the caudal hypothalamus is said to be "temperature-blind". Chemoreceptors of the rostral hypothalamus also influence body temperature, as demonstrated by the febrile response to infiltrated endotoxin [17].

The ability of electrical and chemical stimulation or destruction of areas within the hypothalamus of laboratory animals to produce or inhibit combinations of visceral and somatic motor responses, led to the notion that the hypothalamus is central to the expression of emotional behavioural responses [18]. The well-known 'sham rage' phenomenon observed in response to minimal provocation in decorticate cats, for example, relies on integrity of the posterior hypothalamus and its caudal connections [19].

The hypothalamus is implicated in laughter, the behavioural manifestation of mirth. Foerster and Gagel described discrete bursts of laughter accompanied by whistling, joking and swearing produced repeatedly by the swabbing of blood from the floor of the third ventricle in a patient, after removal of an intraventricular cyst [20]. Lesions in the vicinity of the third ventricular floor producing 'sham mirth' were described by Martin [21], including the case of a young man who laughed uncontrollably at his mother's funeral, and who died from subarachnoid haemorrhage while under investigation for his inappropriate behaviour. He was found to have a ruptured aneurysm at the bifurcation of the basilar artery that compressed the mammillary bodies and elevated the floor of the third ventricle [21]. As discussed by Arroyo *et al.*, a role for the hypothalamus in laughter is strengthened by virtue of the association between HH and gelastic seizures [22]. It has since been shown that the HH itself is the site of origin of gelastic seizures[23] and that the ictal symptoms, including laughter, could be reproduced by electrical stimulation of the HH [24]. However, the role of the hypothalamus proper in the laughter-like vocalisations produced by HH remains uncertain.

Integration of emotional behavioural responses with cognitive processes into an emotional experience was postulated by Papez to be the function of a loop connecting the hippocampus to the mammillary body via the fornix, then via the mammillothalamic tract to the anterior thalamic nucleus, in turn to the cingulate gyrus and then back to the hippocampus [25]. As pointed out by Saper however, each of these structures contains multiple subdivisions with complex connectivity, and credible evidence for the circuitous transfer of information between them is lacking [13]. Nevertheless, the idea has proven extremely influential and has given impetus to research into the structure and function of the limbic system [16].

The fornix and mammillary body are undoubtedly important with respect to memory, but are only two structures among the many interconnected components implicated, many of which are located in the vicinity of the third ventricle [26]. Evidence for the role of the mammillary body comes predominantly from study of the pathological correlates of amnesia in chronic alcoholism, where bilateral destruction of the mammillary bodies is the most consistent finding. However, in patients with Korsakoff psychosis, mammillary body damage is invariably accompanied by involvement of the medial dorsal and posterior thalamic nuclei, the involvement of which is often lacking in alcoholic patients without amnesia [27]. The fornix provides the major efferent pathway from the hippocampal formation (and in particular the subiculum). Disconnection between the hippocampus and mammillary body could therefore be expected to produce memory deficits. Despite conflicting reports concerning the effects of forniceal injury in humans and suggestions that memory impairment need not result from isolated injury even when bilateral [28], a respected review of this literature (and critique of such suggestions) by Gaffan and Gaffan [29] concluded that fornix transection does produce amnesia. In monkeys, lesions of the fornix or mammillary nuclei produce memory impairment that is short-lived when compared to that caused by destruction of the hippocampus [30]; this finding could support an expectation of similarly mild or transient effects of isolated fornix injury in humans. Modality-specific deficits may be produced by unilateral injury according to observations that selective verbal memory impairment follows section of the fornix in the dominant hemisphere [31].

Hypothalamic hamartomas in relation to normal neuroanatomy

Hypothalamic hamartomas have been classified radiologically on the basis of the breadth of attachment to the *tuber cinereum* (sessile *versus* pedunculated) [32], the presence of more than minimal distortion of the outline of the third ventricle (intrahypothalamic *versus* parahypothalamic) [33], or using a combination of size, breadth of attachment, distortion of the hypothalamus and location of attachment (types Ia, Ib, IIa and IIb) [34]. These classifications have attempted to correlate the clinical features observed with the physical properties of the hamartoma. Of interest in relation to these physical properties is the question of what distinguishes a hamartoma associated with seizures, from one without epileptogenic potential. With respect to the surgical treatment of hypothalamic hamartomas causing intractable seizures however, a more important issue may be the determination of that part or attachment of the lesion that is necessary for seizure production or propagation.

The myelinated white matter tracts and nuclei of the hypothalamus (fornices, mammillary bodies and mammillothalamic tracts) are readily visualized with magnetic resonance imaging (MRI) in cadaver brains [35], in normal subjects and in patients with tumours involving these

structures [36]. None of the currently employed classification methods however, consider the attachment of the hamartoma in relation to these intrahypothalamic structures, nor in relation to the above described regions and zones of the hypothalamus. Our observations from a series of more than 50 patients with gelastic seizures (unpublished data) suggest that intraventricular, intrahypothalamic extension of the hamartoma displaces the column of the fornix anterolaterally on the side of predominant attachment. The lateral extent of the intrahypothalamic portion of the lesion is situated between the fornix anteriorly, the mammillary body inferiorly and the mammillothalamic tract posteriorly, and therefore lies predominantly within the mammillary region of the hypothalamus. This detail is often only appreciated with high-resolution, thin-slice T2-weighted images in three planes through the hypothalamus and HH *(figure 2)*. The importance of the intrahypothalamic connections of HH associated with seizures is a subject of great interest, having potential implications for mechanisms of epileptogenesis (how partial and secondary generalised seizures develop), and requires consideration when devising surgical strategies for the management of intractable epilepsy in these patients.
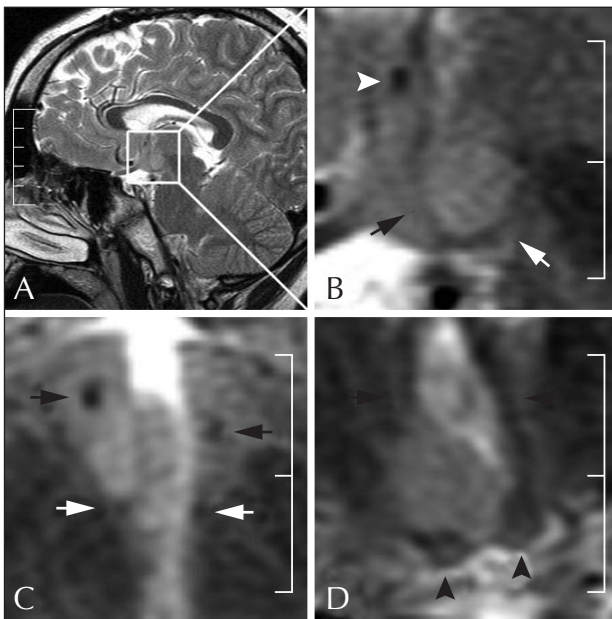

Figure 2. Anatomy of a small hypothalamic hamartoma.
(A) Parasagittal T2-weighted magnetic resonance image (TE 6200, TR 100.5, 3 mm thickness) at the level of the right fornix and mammillothalamic tract, with a magnified view of the same image in the right-hand panel (B), and magnified T2-weighted axial (C) and coronal (D) images below.
The images clearly show the myelinated anterior commissure (white arrowhead), fornices (black arrows), mammillothalamic tracts (white arrows) and mammillary bodies (black arrowheads) in relation to the HH, with displacement of the right fornix anteriolaterally (C) and the right mammillary body inferiorly (D).

Embryology of the hypothalamus and hamartomas

Forebrain development

Early models of forebrain development were based on the appearance and transformation of sulci and ridges along the ventricular and pial surfaces of the developing brain [37], and the hypothalamus was regarded as the ventral-most derivative of 'longitudinally' arranged histogenic columns in the diencephalon (along with the thalamus and epithalamus dorsally) [38, 39]. However, fate-mapping studies of the neural plate showed that the hypothalamus is derived from the anterior-most parts of the neuraxis [40, 41]. In addition, assimilation of information concerning the expression of transcription factors in the developing brain suggested a segmental organisation of the forebrain comparable to that found in the hindbrain and spinal cord [42, 43].

In the segmental 'prosomeric' model, the basal and alar plates extend to the anterior-most part of the brain [44] and the hypothalamus is not derived from the diencephalon, but from ventral aspects of the two or three rostral segments of the neural tube (secondary prosencephalon), the dorsal derivatives of which form the telencephalon. According to the current formulation of the model, an alar 'prethalamic' region of the secondary prosencephalon contains the preoptic, supraoptic-paraventricular, suprachiasmatic, anterior, periforniceal and dorsal parts of the hypothalamus, while the retrochiasmatic, median eminence, ventral, infundibular and mammillary regions of the hypothalamus are derived from the basal and floor plate parts of the same prosomeres [45]. A comparison of the pervasive columnar model and the increasingly refined prosomeric model is shown in *figure 3*. For greater detail, the reader is referred to a review by one of the proponents of the prosomeric model [45].

Descriptive embryology of the human hypothalamus

Despite reservations about the significance of ventricular sulci and ridges, direct knowledge of human brain development is largely confined to descriptions of these, together with some information regarding the anlagen of nuclei and fibre tracts. In the absence of a known sequence and timing of cellular mechanisms, these morphological data might assist in roughly pinpointing abnormal development. The authors of the first descriptions of the Pallister-Hall syndrome, for example, used the descriptive embryology and the presence or absence of other hypothalamic and pituitary anomalies to suggest that the large HH associated with the neonatally lethal form of this disease develop in the fifth week of gestation [46, 47]. A summary of descriptive embryological milestones for the hypothalamus is presented in *table 2*, based on Muller and O'Rahilly's studies of the Carnegie collection of human embryos [37, 48-53], in which described stages depend
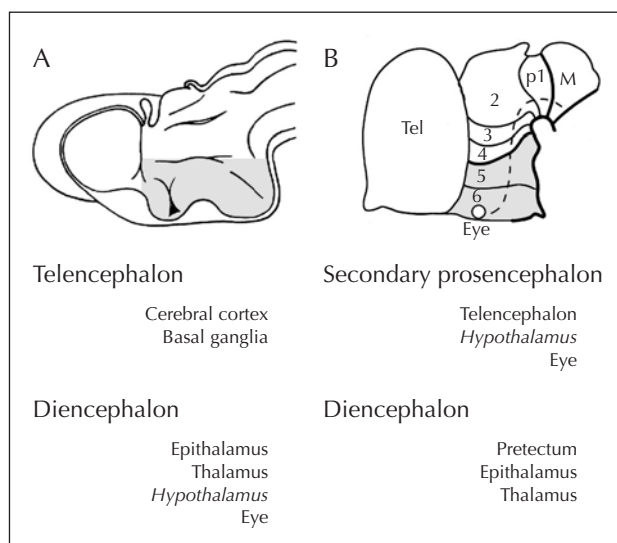
Figure 3. Comparison of two models of forebrain development in relation to the derivation of the hypothalamus (shaded areas).
To the left is the columnar model (A) and at right (B), the prosomeric model. Note that a fundamental difference between the two is in the specification of the longitudinal axis of the forebrain, shown by the horizontal arrangement of the diencephalic sulci in the columnar model and by the dashed line, representing the alar/basal boundary, in the prosomeric model. The nomenclature applicable to each model is shown below. Modified from Kuhlenbeck and Haymaker [38] and Puelles [45].

on morphological criteria corresponding to a range of post-fertilization ages [54].

Developmental biology of the hypothalamus

The relationship between the pituitary gland and hypothalamus in development has been clarified by laboratory animal evidence showing that the whole of the pituitary (including the anterior pituitary precursor Rathke's pouch, formerly thought of as an epithelial structure) is derived

Table 2. Descriptive embryology of the human hypothalamus

CS	DPC	Morphological milestone
IX	25	Three primary brain divisions visible in open neural folds
X	28	Optic sulcus visible; neural tube begins to fuse
XI	29	Closure of rostral neuropore is complete
XII	30	Infundibular hypothalamus indicated by relation to Rathke's pouch
XIII	32	Mammillary recess identified
XIV	33	Hypothalamic cell cord identified
XV	36	Appearance of mammillary nuclei and MTT fibres
XVII	41	Supra- and inframammillary recesses define the mammillary area

CS = Carnegie stage of development; **DPC** = approximate days post-conception; **MTT** = mammillotegmental tract.

from the anterior neural ridge [55], and that the adjacent neural plate gives rise to the hypothalamus [40]. Some cells of the hypothalamus proper arise in structures of anterior neural ridge origin but take an extracerebral route to their final destination [56]; luteinising-hormone-releasing hormone – (LHRH) producing cells, for example, originate in the olfactory placode and then migrate to the septal region, anterior hypothalamus and median eminence [57].

Genetic mechanisms that underlie hypothalamic development are beginning to be unravelled. As reviewed by Michaud, the program of development progresses from induction and patterning of the hypothalamus by the axial mesendoderm, to the differentiation of specific hypothalamic nuclei [58]. At present, considerably more is known about development of the hypothalamic-pituitary axis than about other hypothalamic structures, just as knowledge of the function of the hypothalamus is more advanced in relation to neurendocrine aspects.

Sonic hedgehog protein (SHH) is a concentration-dependent morphogen that is produced by the axial mesendoderm and plays a crucial role in dorso-ventral patterning of the neuraxis along its length, by regulating the expression of a large number of homeodomain proteins [59]. It is the major known factor in ventralisation of the developing forebrain and its expression by the underlying prechordal plate is a requirement for appearance of the hypothalamic anlage, and splitting of the eye field into two [60]. SHH-dependent Nkx-2.1 expression [61] demarcates the primordial hypothalamus as early as the three-somite stage in mice (equivalent Carnegie stage IX) [44], and is required for the normal development of the anterior pituitary as well as many hypothalamic nuclei, including those in the mammillary region [62]. In addition, SHH appears to influence both proliferation and cell-type determination in the developing pituitary gland [63].

In the hypothalamic-pituitary axis, differentiation of specific cell types progresses in an orderly fashion, controlled by a hierarchy of transcription factors expressed in a spatially and temporally restricted sequence. Factors involved in pituitary specification include Rpx (Rathke's pouch homeobox), Six3, Pax6, Lhx3, Ptx1, Pit-1 and SF-1. Development of cell phenotype in the supraoptic, paraventricular, periventricular and arcuate nuclei is regulated by factors including Sim1, Arnt2, Otp, Brn2, and Gsh1. Treier and Rosenfeld reviewed the topic of hypothalamic-pituitary co-development in detail [64]; more recent information concerning neurendocrine hypothalamic differentiation was summarised by Acampora *et al.* [65].

Although the precise mechanisms of hypothalamic nuclear specification are unknown, the number of transcription factors implicated continues to increase. These include: Fhx5, essential for mammillary body development [66]; Pax6, required for mammillothalamic tract

development and axon path finding [67]; Wnt8b, expressed in the mammillary region of human embryos [68]; and SF-1, necessary for normal development of the ventromedial nucleus [69]. Further study of these and other factors may answer questions about normal and abnormal hypothalamic development.

Development of hypothalamic hamartomas

The embryological origin of HH has not been determined. Histological examination of hamartoma biopsy material from patients with epilepsy has shown a mixture of mature neuronal and glial cells [70], with some myelinated fibres present [71] and an overall resemblance to normal hypothalamic grey matter [32]. Hamartomas associated with precocious puberty have been shown to contain neurosecretory granules and immunoreactive staining with antibodies to LHRH [72], including one child with the combination of gelastic seizures and precocious puberty [73]. In two other cases with precocious puberty alone, LHRH was not found, but transforming growth factor alpha and its receptor were present [74]. A detailed study of HH cell characteristics with respect to normal hypothalamic nuclear cytoarchitecture and immunohistochemistry in a large series is awaited.

A relatively small number of potentially harmful prenatal exposures have been accepted as causing brain malformation, with some known to produce specific malformations of cortical development (MCD). Examples of the latter include viral infections such as cytomegalovirus, ionising radiation, medications such as isotretinoin, alcohol, illicit drugs such as cocaine, and toxins such as methylmercury [75-78]. Only two case-control studies of MCD are reported in the literature. The first involved mainly adult epilepsy surgery patients, comparing those with and without MRI evidence of MCD, and found that mothers of patients with MCD were more likely to have been exposed to injury, medication, infection, or irradiation during pregnancy than were mothers of patients without MCD [79]. The second study found a higher rate of antenatal maternal exposure to medication, alcohol and potential toxins among paediatric epilepsy surgery patients with histological evidence of MCD, as compared to age-matched, neurologically normal controls [80]. Together, these provide some evidence for the importance of environmental factors in the pathogenesis of MCD, although neither study included patients with HH. Potential environmental antecedents to the development of HH deserve some attention and, given the rarity of the malformation, a case-control study would be appropriate.

There are a number of multiple congenital anomaly syndromes in which HH have been described, but in only one of these – Pallister-Hall syndrome (PHS) – is the HH a characteristic feature and required for the diagnosis of an index case [81]. Along with central polydactyly, associated malformations in PHS include dysplastic nails, pitu-

itary hypoplasia or dysfunction, bifid epiglottis and imperforate anus [82]. Autosomal-dominant transmission of PHS is described [83], and in some families a mutation in the Gli3 gene on chromosome 7p13 is present [84]. Gli proteins are zinc-finger transcription factors that act downstream of SHH-signalling to regulate target-gene expression [85]. As discussed by Michaud, the mechanism by which Gli3 frameshift mutation leads to HH formation is currently unknown, but may be related to either gain or loss of normal Gli3 function as an inhibitor of SHH-signalling [58].

One case report of the cytogenetic evaluation of an HH in a patient with PHS, cited by Biesecker and Graham [82], showed the absence of chromosome 17 in two of 43 cells, but no similar studies on HH tissue are described. One patient with HH and microphthalmia, but not polydactyly, was found to have an unbalanced chromosome 7 translocation that did not involve the Gli3 locus [86]. Other entities, probably distinct from PHS, in which HH have been reported include the McKusick-Kaufman syndrome [87], Bardet-Biedl syndrome [88], oral-facial-digital syndrome type 6 [89] and Waardenburg syndrome [90]; of interest in relation to the first two conditions is that one form of Bardet-Biedl syndrome has a mutation in the gene associated with McKusick-Kaufman syndrome (MKKS) on chromosome 20p12 [91]. It is quite possible that genetic factors in the development of syndrome-associated HH could play a part in the development of sporadic, non-syndrome-associated HH, however no clinical or molecular genetic studies of such patients have been reported. Cytogenetic and molecular genetic evaluation of biopsied HH material might also prove rewarding in this respect.

It is likely that both the anatomical position and the intrinsic epileptogenicity of HH associated with seizures together contribute to the various neurological disorders associated with HH [92]. Appreciation of the normal functional anatomy of the hypothalamus, the structural relationship and connectivity between HH and adjacent hypothalamic nuclei and fibre pathways, and visualisation of this with high-quality MRI is necessary for understanding the clinical manifestations of HH and in predicting potential complications that may result from HH surgery. The anatomo-clinical correlation may contribute to questions about the mechanisms of epileptogenesis, reasons for cognitive deficits and the nature of behavioural and psychiatric disturbance.

While the cause of sporadic HH development is not known, there is considerable effort currently invested in understanding normal development of the human hypothalamus, and this will undoubtedly contribute to a better appreciation of abnormal development. The most promising avenue for further investigation in this respect is the exploration of the mechanisms of HH development in genetically determined, syndrome-associated HH.

References

1. List CF, Dowman CE, Bagchi BK, *et al.* Posterior hypothalamic hamartomas and gangliogliomas causing precocious puberty. *Neurology* 1958; 8: 164-74.

2. Berkovic SF, Andermann F, Melanson D, *et al.* Hypothalamic hamartomas and ictal laughter: evolution of a characteristic epileptic syndrome and diagnostic value of magnetic resonance imaging. *Ann Neurol* 1988; 23: 429-39.

3. Deonna T, Ziegler AL. Hypothalamic hamartoma, precocious puberty and gelastic seizures: a special model of 'epileptic' developmental disorder. *Epileptic Disord* 2000; 2: 33-7.

4. Frattali CM, Liow K, Craig GH *et al.* Cognitive deficits in children with gelastic seizures and hypothalamic hamartoma. *Neurology* 2001; 57: 43-6.

5. Weissenberger AA, Dell ML, Liow K, *et al.* Aggression and psychiatric comorbidity in children with hypothalamic hamartomas and their unaffected siblings. *J Am Acad Child Adolesc Psychiatry* 2001; 40: 696-703.

6. Nauta WJH, Haymaker W. Hypothalamic nuclei and fiber connections. In: Haymaker W, Anderson E, Nauta WJH. *The hypothalamus.* Springfield: Thomas, 1969: 136-209.

7. Truex RC, Carpenter MB. The diencephalon and corpus striatum. In: Truex RC, Carpenter MB. *Human Neuroanatomy.* Baltimore: Williams and Wilkins, 1964: 379-442.

8. Crosby EC, Showers MJC. Comparative anatomy of the preoptic and hypothalamic areas. In: Haymaker W, Anderson E, Nauta WJH. *The hypothalamus.* Springfield: Thomas, 1969: 61-135.

9. Braak H, Braak E. Anatomy of the human hypothalamus (chiasmatic and tuberal region). *Prog Brain Res* 1992; 93: 3-14.

10. Kuhlenbeck H, Christ JF. Derivation and boundaries of the hypothalamus, with atlas of hypothalamic grisea. In: Haymaker W, Anderson E, Nauta WJH. *The hypothalamus.* Springfield: Thomas, 1969: 13-60.

11. Swanson LW. The neuroanatomy revolution of the 1970s and the hypothalamus. *Brain Res Bull* 1999; 50: 397.

12. Swaab DF. Development of the human hypothalamus. *Neurochem Res* 1995; 20: 509-19.

13. Saper CB. Hypothalamic connections with the cerebral cortex. *Prog Brain Res* 2000; 126: 39-48.

14. Holman SD, Janus C. Laterally asymmetrical cell number in a sexually dimorphic nucleus in the gerbil hypothalamus is correlated with vocal emission rates. *Behav Neurosci* 1998; 112: 979-90.

15. Moore RY. The organization of the human circadian timing system. *Prog Brain Res* 1992; 93: 99-115.

16. Nolte J. Drives, emotions and memories: the hypothalamus and limbic system. *The human brain: an introduction to its functional anatomy.* St. Louis: Mosby, 1999: 537-63.

17. Meyers RD. Temperature regulation: neurochemical systems in the hypothalamus. In: Haymaker W, Anderson E, Nauta WJH. *The hypothalamus.* Springfield: Thomas, 1969: 506-23.

18. MacLean PD. The hypothalamus and emotional behavior. In: Haymaker W, Anderson E, Nauta WJH. *The hypothalamus.* Springfield: Thomas, 1969: 659-78.

19. Bard P. A diencephalic mechanism for the expression of rage with special reference to the sympathetic nervous system. *Am J Physiol* 1928; 84: 490-515.

20. Foerster O, Gagel O. Ein fall von ependymcyste des III. ventrikels. Ein beitrag zur frage der beziehungen psychischer störungen zum hirnstamm. *Z ges Neurol Psychiatr* 1933; 149: 312-44.

21. Martin JP. Fits of laughter (sham mirth) in organic cerebral disease. *Brain* 1950; 73: 453-64.

22. Arroyo S, Lesser RP, Gordon B *et al.* Mirth, laughter and gelastic seizures. *Brain* 1993; 116 (Pt 4): 757-80.

23. Munari C, Kahane P, Francione S *et al.* Role of the hypothalamic hamartoma in the genesis of gelastic fits (a video-stereo-EEG study).*Electroencephalogr Clin Neurophysiol* 1995; 95: 154-60.

24. Kuzniecky R, Guthrie B, Mountz J *et al.* Intrinsic epileptogenesis of hypothalamic hamartomas in gelastic epilepsy. *Ann Neurol* 1997; 42: 60-7.

25. Papez JW. A proposed mechanism of emotion. *Arch Neurol Psychiatr* 1937; 38: 725-43.

26. Damasio AR, Van Hoesen GW, Tranel D. Pathological correlates of amnesia and the anatomical basis of memory. In: Apuzzo MLJ. *Surgery of the third ventricle.* Baltimore: Williams and Wilkins, 1998: 187-204.

27. Adams RD, Victor M. Diseases of the nervous system due to nutritional deficiency. *Principles of Neurology.* New York: McGraw-Hill, 1989: 820-45.

28. Garcia-Bengochea F, Friedman WA. Persistent memory loss following section of the anterior fornix in humans. A historical review. *Surg Neurol* 1987; 27: 361-4.

29. Gaffan D, Gaffan EA. Amnesia in man following transection of the fornix. A review. *Brain* 1991; 114 (Pt 6): 2611-8.

30. Zola-Morgan S, Squire LR, Amaral DG. Lesions of the hippocampal formation but not lesions of the fornix or the mammillary nuclei produce long-lasting memory impairment in monkeys. *J Neurosci* 1989; 9: 898-913.

31. Hodges JR, Carpenter K. Anterograde amnesia with fornix damage following removal of IIIrd ventricle colloid cyst. *J Neurol Neurosurg Psychiatry* 1991; 54: 633-8.

32. Boyko OB, Curnes JT, Oakes WJ *et al.* Hamartomas of the tuber cinereum: CT, MR, and pathologic findings. *AJNR Am J Neuroradiol* 1991; 12: 309-14.

33. Arita K, Ikawa F, Kurisu K, *et al.* The relationship between magnetic resonance imaging findings and clinical manifestations of hypothalamic hamartoma. *J Neurosurg* 1999; 91: 212-20.

34. Valdueza JM, Cristante L, Dammann O, *et al.* Hypothalamic hamartomas: with special reference to gelastic epilepsy and surgery. *Neurosurgery* 1994; 34: 949-58.

35. Miller MJ, Mark LP, Yetkin FZ, *et al.* Imaging white matter tracts and nuclei of the hypothalamus: an MR- anatomic comparative study. *AJNR Am J Neuroradiol* 1994; 15: 117-21.

36. Saeki N, Sunami K, Kubota M, *et al.* Heavily T2-weighted MR imaging of white matter tracts in the hypothalamus: normal and pathologic demonstrations. *AJNR Am J Neuroradiol* 2001; 22: 1468-75.

37. Muller F, O'Rahilly R. The timing and sequence of appearance of neuromeres and their derivatives in staged human embryos. *Acta Anat (Basel)* 1997; 158: 83-99.

38. Kuhlenbeck H, Haymaker W. The derivatives of the hypothalamus in the human brain; their relation to the extrapyramidal and autonomic nervous system. *Milit Surg* 1949; 105: 26.

39. Kuhlenbeck H. Overall morphologic pattern. *The central nervous system of vertebrates: a general survey of its comparative anatomy with an introduction to the pertinent fundamental biologic and logical concepts.* Basel: S.Karger, 1973.

40. Couly G, Le Douarin NM. The fate map of the cephalic neural primordium at the presomitic to the 3-somite stage in the avian embryo. *Development* 1988; 103 Suppl: 101-13.

41. Eagleson GW, Harris WA. Mapping of the presumptive brain regions in the neural plate of Xenopus laevis. *J Neurobiol* 1990; 21: 427-40.

42. Puelles L, Rubenstein JL. Expression patterns of homeobox and other putative regulatory genes in the embryonic mouse forebrain suggest a neuromeric organization. *Trends Neurosci* 1993; 16: 472-9.

43. Rubenstein JL, Martinez S, Shimamura K, *et al.* The embryonic vertebrate forebrain: the prosomeric model. *Science* 1994; 266: 578-80.

44. Shimamura K, Hartigan DJ, Martinez S, *et al.* Longitudinal organization of the anterior neural plate and neural tube. *Development* 1995; 121: 3923-33.

45. Puelles L. Brain segmentation and forebrain development in amniotes. *Brain Res Bull* 2001; 55: 695-710.

46. Hall JG, Pallister PD, Clarren SK *et al.* Congenital hypothalamic hamartoblastoma, hypopituitarism, imperforate anus and postaxial polydactyly – a new syndrome? Part I: clinical, causal, and pathogenetic considerations. *Am J Med Genet* 1980; 7: 47-74.

47. Clarren SK, Alvord EC, Jr., Hall JG. Congenital hypothalamic hamartoblastoma, hypopituitarism, imperforate anus, and postaxial polydactyly – a new syndrome? Part II: Neuropathological considerations. *Am J Med Genet* 1980; 7: 75-83.

48. Muller F, O'Rahilly R. The first appearance of the neural tube and optic primordium in the human embryo at stage 10. *Anat Embryol (Berl)* 1985; 172: 157-69.

49. Muller F, O'Rahilly R. The development of the human brain, the closure of the caudal neuropore, and the beginning of secondary neurulation at stage 12. *Anat Embryol (Berl)* 1987; 176: 413-30.

50. Muller F, O'Rahilly R. The development of the human brain from a closed neural tube at stage 13. *Anat Embryol (Berl)* 1988; 177: 203-24.

51. Muller F, O'Rahilly R. The development of the human brain, including the longitudinal zoning in the diencephalon at stage 15. *Anat Embryol (Berl)* 1988; 179: 55-71.

52. Muller F, O'Rahilly R. The human brain at stage 17, including the appearance of the future olfactory bulb and the first amygdaloid nuclei. *Anat Embryol (Berl)* 1989; 180: 353-69.

53. O'Rahilly R, Muller F. *The embryonic human brain: an atlas of developmental stages.* New York: Wiley-Liss, 1994.

54. O'Rahilly R, Muller F. Minireview: summary of the initial development of the human nervous system. *Teratology* 1999; 60: 39-41.

55. Kawamura K, Kikuyama S. Evidence that hypophysis and hypothalamus constitute a single entity from the primary stage of histogenesis. *Development* 1992; 115: 1-9.

56. Kawamura K, Kikuyama S. Morphogenesis of the hypothalamus and hypophysis: their association, dissociation and reassociation before and after "Rathke". *Arch Histol Cytol* 1998; 61: 189-98.

57. Schwanzel-Fukuda M. Origin and migration of luteinizing hormone-releasing hormone neurons in mammals. *Microsc Res Tech* 1999; 44: 2-10.

58. Michaud JL. The developmental program of the hypothalamus and its disorders. *Clin Genet* 2001; 60: 255-63.

59. Marti E, Bovolenta P. Sonic hedgehog in CNS development: one signal, multiple outputs. *Trends Neurosci* 2002; 25: 89-96.

60. Pera EM, Kessel M. Patterning of the chick forebrain anlage by the prechordal plate. *Development* 1997; 124: 4153-62.

61. Pabst O, Herbrand H, Takuma N, *et al.* NKX2 gene expression in neuroectoderm but not in mesendodermally derived structures depends on sonic hedgehog in mouse embryos. *Dev Genes Evol* 2000; 210: 47-50.

62. Kimura S, Hara Y, Pineau T, *et al.* The T/ebp null mouse: thyroid-specific enhancer-binding protein is essential for the organogenesis of the thyroid, lung, ventral forebrain, and pituitary. *Genes Dev* 1996; 10: 60-9.

63. Treier M, O'Connell S, Gleiberman A, *et al.* Hedgehog signaling is required for pituitary gland development. *Development* 2001; 128: 377-86.

64. Treier M, Rosenfeld MG. The hypothalamic-pituitary axis: co-development of two organs. *Curr Opin Cell Biol* 1996; 8: 833-43.

65. Acampora D, Postiglione MP, Avantaggiato V, *et al.* Progressive impairment of developing neuroendocrine cell lineages in the hypothalamus of mice lacking the Orthopedia gene. *Genes Dev* 1999; 13: 2787-800.

66. Wehr R, Mansouri A, de Maeyer T *et al.* Fkh5-deficient mice show dysgenesis in the caudal midbrain and hypothalamic mammillary body. *Development* 1997;124:4447-56.

67. Valverde F, Garcia C, Lopez-Mascaraque L, *et al.* Development of the mammillothalamic tract in normal and Pax-6 mutant mice. *J Comp Neurol* 2000; 419: 485-504.

68. Lako M, Lindsay S, Bullen P, *et al.* A novel mammalian wnt gene, WNT8B, shows brain-restricted expression in early development, with sharply delimited expression boundaries in the developing forebrain. *Hum Mol Genet* 1998; 7: 813-22.

69. Dellovade TL, Young M, Ross EP, *et al.* Disruption of the gene encoding SF-1 alters the distribution of hypothalamic neuronal phenotypes. *J Comp Neurol* 2000; 423: 579-89.

70. Rosenfeld JV, Harvey AS, Wrennall J, *et al.* Transcallosal resection of hypothalamic hamartomas, with control of seizures, in children with gelastic epilepsy. *Neurosurgery* 2001; 48: 108-18.

71. Paillas JE, Roger J, Toga M, *et al.* Hamartome de l'hypothalmus: étude clinique, radiologique, histologique: résultats de l'exèrèse. *Rev Neurol (Paris)* 1969; 120: 177-94.

72. Judge DM, Kulin HE, Page R, *et al.* Hypothalamic hamartoma: a source of luteinizing-hormone-releasing factor in precocious puberty. *N Engl J Med* 1977; 296: 7-10.

73. Culler FL, James HE, Simon ML, *et al.* Identification of gonadotropin-releasing hormone in neurons of a hypothalamic hamartoma in a boy with precocious puberty. *Neurosurgery* 1985; 17: 408-12.

74. Jung H, Carmel P, Schwartz MS *et al.* Some hypothalamic hamartomas contain transforming growth factor alpha, a puberty-inducing growth factor, but not luteinizing hormone-releasing hormone neurons. *J Clin Endocrinol Metab* 1999; 84: 4695-701.

75. Choi BH. The effects of methylmercury on the developing brain. *Prog Neurobiol* 1989; 32: 447-70.

76. Hayward JC, Titelbaum DS, Clancy RR, *et al.* Lissencephaly-pachygyria associated with congenital cytomegalovirus infection. *J Child Neurol* 1991; 6: 109-14.

77. Jones KL. *Smith's recognizable patterns of human malformation*. 5th ed. Philadelphia: W.B. Saunders, 1997.

78. Volpe JJ. Teratogenic effects of drugs and passive addiction. *Neurology of the newborn*. Philadelphia: W.B. Saunders, 2001: 859-98.

79. Palmini A, Andermann E, Andermann F. Prenatal events and genetic factors in epileptic patients with neuronal migration disorders. *Epilepsia* 1994; 35: 965-73.

80. Dean P, Harvey AS, Bean J, *et al.* Antecedents of developmental neuropathology: a case-control study in surgically-treated children with intractable partial epilepsy. *Epilepsia* 1996; 37: S104. (Abstract)

81. Biesecker LG, Abbott M, Allen J, *et al.* Report from the workshop on Pallister-Hall syndrome and related phenotypes. *Am J Med Genet* 1996; 65: 76-81.

82. Biesecker LG, Graham JM, Jr. Pallister-Hall syndrome. *J Med Genet* 1996;33:585-9.

83. Topf KF, Kletter GB, Kelch RP, *et al.* Autosomal dominant transmission of the Pallister-Hall syndrome. *J Pediatr* 1993; 123: 943-6.

84. Kang S, Graham JM, Jr., Olney AH, *et al.* GLI3 frameshift mutations cause autosomal dominant Pallister-Hall syndrome. *Nat Genet* 1997; 15: 266-8.

85. Villavicencio EH, Walterhouse DO, Iannaccone PM. The sonic hedgehog-patched-gli pathway in human development and disease. *Am J Hum Genet* 2000; 67: 1047-54.

86. Kuller JA, Cox VA, Schonberg SA, *et al.* Pallister-Hall syndrome associated with an unbalanced chromosome translocation. *Am J Med Genet* 1992; 43: 647-50.

87. Unsinn KM, Neu N, Krejci A, *et al.* Pallister-Hall syndrome and McKusick-Kaufmann syndrome: one entity? *J Med Genet* 1995; 32: 125-8.

88. Diaz LL, Grech KF, Prados MD. Hypothalamic hamartoma associated with Laurence-Moon-Biedl syndrome. Case report and review of the literature. *Pediatr Neurosurg* 1991; 17: 30-3.

89. Stephan MJ, Brooks KL, Moore DC, *et al.* Hypothalamic hamartoma in oral-facial-digital syndrome type VI (Varadi syndrome). *Am J Med Genet* 1994; 51: 131-6.

90. Sener RN. Cranial MR imaging findings in Waardenburg syndrome: anophthalmia, and hypothalamic hamartoma. *Comput Med Imaging Graph* 1998; 22: 409-11.

91. Slavotinek AM, Stone EM, Mykytyn K, *et al.* Mutations in MKKS cause Bardet-Biedl syndrome. *Nat Genet* 2000; 26: 15-6.

92. Berkovic SF, Kuzniecky RI, Andermann F. Human epileptogenesis and hypothalamic hamartomas: new lessons from an experiment of nature. *Epilepsia* 1997; 38: 1-3.