# The Hypothalamus and Hypothalamohypophysial Systems

13

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## Contents



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## 13.1 Introduction

The rather small hypothalamus contains a large number of more or less well-defined cell groups that are of utmost importance for preserving the individual and the species. The hypothalamus is involved in a wide variety of functions in the brain and is characterized by numerous connections with practically every major part of the central nervous system (CNS), including the cerebral cortex, the hippocampus, the amygdala, the thalamus, the cerebellum, the brain stem and the spinal cord. Alterations in hypothalamic nuclei are found in various endocrine diseases such as diabetes insipidus (DI), Wolfram and Prader–Willi syndromes, and in various neurodegenerative diseases such as Alzheimer, Parkinson and Huntington diseases. In two volumes of the *Handbook of Clinical Neurology*, Dick Swaab described almost everything so far known about the hypothalamus and its role in health and disease (Swaab 2003, 2004). This chapter merely represents a brief summary of these volumes.

Through its intimate neuronal and vascular relationships with the pituitary gland, the hypothalamus controls the release of the pituitary hormones, thereby bringing the entire endocrine system under the control of the CNS. In 1940, Ernst and Berta Scharrer presented their findings on neurosecretory neurons in the hypothalamus that secrete hormones directly into the blood stream (Scharrer and Scharrer 1940). In 1949, Wolfgang Bargmann presented the first evidence for a **magnocellular secretory system**, composed of supraoptic and paraventricular neurons, giving rise to axons that innervate the posterior lobe of the pituitary via the tuberohypophysial tract (Bargmann 1949). All other hypothalamic control of pituitary function is achieved through neurohumoral mechanisms via the portal plexus in the external zone of the median eminence. Neurosecretory neurons throughout the hypothalamus, more in particular the arcuate nucleus, project to the median eminence. This **parvocellular secretory system** controls the anterior pituitary.

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The hypothalamus is concerned with generalized response patterns that often involve autonomic, somatomotor and endocrine systems. The classic experiments by Bard (1928, 1929) and Hess (1936) and Hess and Brügger (1943) have shown that by electrical stimulation characteristic behavioural patterns related to feeding, fear, attack, rage and reproduction can be elicited from different hypothalamic structures. A combination of immunocytochemical mapping of *c-Fos* and related immediately early genes (see Chap. 3) with tract-tracing techniques has been widely used to elucidate the neural substrate of different kinds of behaviour. Following a brief description of the boundaries and subdivision of the hypothalamus (Sect. 13.2), the hypothalamic fibre connections with the CNS (Sect. 13.3) and with the hypophysis (Sect. 13.4), and aspects of the functional organization of the hypothalamus such as the control of feeding, reproduction, thermoregulation and sleep (Sect. 13.5) will be discussed. Damage to different parts of the hypothalamohypophysial system may result in various neuroendocrine disturbances. Autonomic dysfunctions in the respiratory, cardiovascular and gastrointestinal systems are commonly seen, as are disturbances in temperature regulation, water balance, sexual behaviour and food intake. Hypothalamic lesions can also change the level of consciousness, the sleep–wake cycle (see Chap. 5) and emotional behaviour (see Chap. 14). Many pathological processes can damage the hypothalamus, most common are tumours of the pituitary. Pituitary tumours become clinically evident through problems caused by: (1) their enlargement, such as pressure on the optic chiasm or one of the optic tracts (see Chap. 8) or lateral growth into the cavernous sinus, resulting in dysfunction of one or several of the ocular motor nerves and the ophthalmic division of the trigeminal nerve (see Chap. 6); (2) oversecretion of hormones and (3) inadequate secretion of hormones. Some examples are presented as ***Clinical cases***.

## 13.2 Anatomical Organization

The hypothalamus was first identified as a separate division of the diencephalon by His (1893). Since the early studies by Gurdjian (1927), Krieg (1932) and Le Gros Clark (1936, 1938), the hypothalamus is subdivided into four regions, from caudal to rostral: (1) the mammillary region; (2) the tuberal region; (3) the anterior complex and (4) the preoptic region. The latter two regions are usually grouped together as the chiasmatic or preoptic region. From a developmental point of view, however, three longitudinal subdivisions of the hypothalamus can be distinguished (Angevine 1970; Altman and Bayer 1986: Mai and Ashwell 2004) as originally proposed by Crosby and Woodburne (1940): a periventricular zone, an intermediate or medial zone and a lateral zone. The entire hypothalamus is now thought to arise from that part of the secondary prosencephalon that is known as the rostral diencephalon and, therefore, is sometimes considered to be part of the telencephalon. Its boundaries and subdivision are discussed in Sect. 13.2.1, the hypothalamic nuclei in Sect. 13.2.2 and the pituitary gland in Sect. 13.2.3. Closely related to the hypothalamus are circumventricular organs (CVOs) such as the median eminence (Sect. 13.2.4).

### 13.2.1 Boundaries and Subdivision

The hypothalamus is located below the thalamus and separated from it by the hypothalamic sulcus (Fig. 13.1). The lamina terminalis is usually viewed as the rostral boundary of the hypothalamus, whereas an imaginary line from the posterior commissure to the caudal border of the mammillary body marks the caudal boundary. Dorsolaterally, the hypothalamus extends above the hypothalamic sulcus as far as the medial edge of the corpus callosum. Rostrally, the hypothalamus is continuous with the preoptic and septal areas in the mediobasal parts of the forebrain and with the sublenticular part of the substantia innominata. Caudally, the hypothalamus is continuous with the central grey and the tegmentum of the mesencephalon. The basal part of the hypothalamus is characterized by the two **mammillary bodies** caudally, the optic chiasm rostrally and the tuber cinereum in between (Fig. 13.2). The **tuber cinereum** (the grey swelling) tapers ventrally into the **infundibulum** which forms the most proximal part of the neurohypophysis. The infundibulum and the infundibular part of the adenohypophysis together form the **hypophysial stalk**. Based on these conspicuous basal landmarks, the hypothalamus can be divided into three parts: an anterior, chiasmatic or supraoptic part, a middle, tuberal part and a posterior, mammillary part (Fig. 13.3).

The **arterial supply** of the preoptic and anterior parts of the hypothalamus comes mainly from the anterior cerebral and anterior communicating arteries, whereas the tuberal region and the posterior hypothalamus are mainly supplied by the posterior communicating artery (Haymaker 1969). The posterior hypothalamus also receives branches from the basilar and posterior cerebral arteries. The **venous drainage** of the hypothalamus goes via the anterior cerebral vein, the basal vein of Rosenthal and the internal cerebral vein to the great cerebral vein of Galen. The hypothalamus, in particular its anterior part, is occasionally damaged by the rupture of an aneurysm of the circle of Willis (Crompton 1963). The pituitary is supplied by the superior and inferior hypophysial arteries (Haymaker 1969; Daniel and Pritchard 1975; Gebarski 1993).

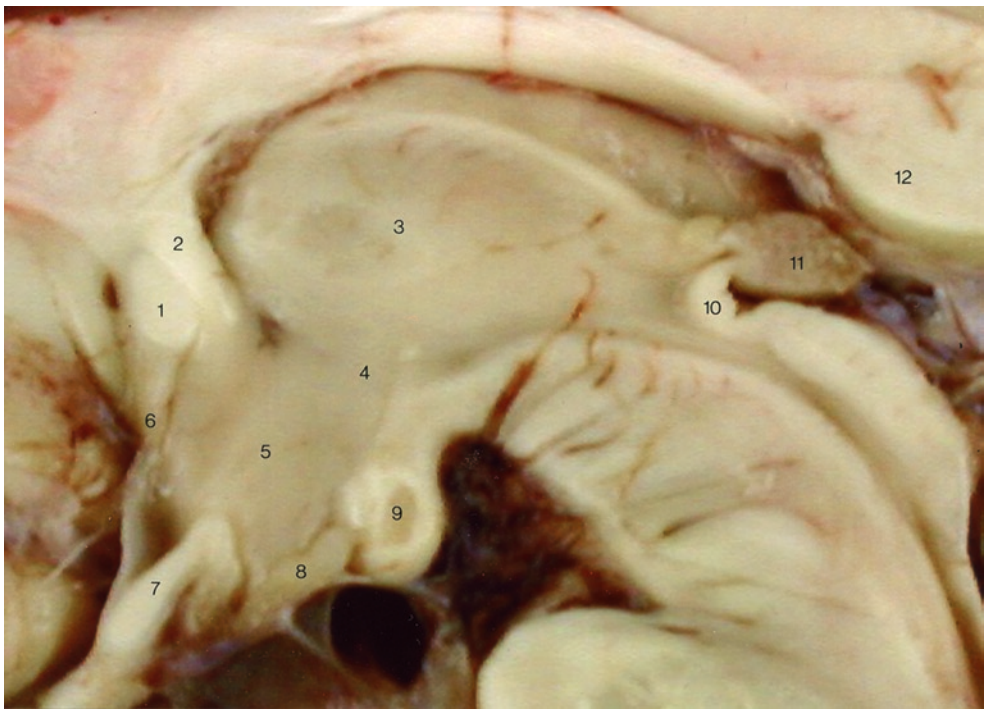


**Fig. 13.1** Median section of the brain, showing the relations of the hypothalamus. The following structures are indicated by numbers: (1) anterior commissure; (2) fornix; (3) thalamus; (4) hypothalamic sulcus; (5) hypothalamus; (6) l amina terminalis; (7) optic chiasm; (8) tuber cinereum; (9) mammillary body; (10) posterior commissure; (11) pineal gland; (12) splenium of corpus callosum

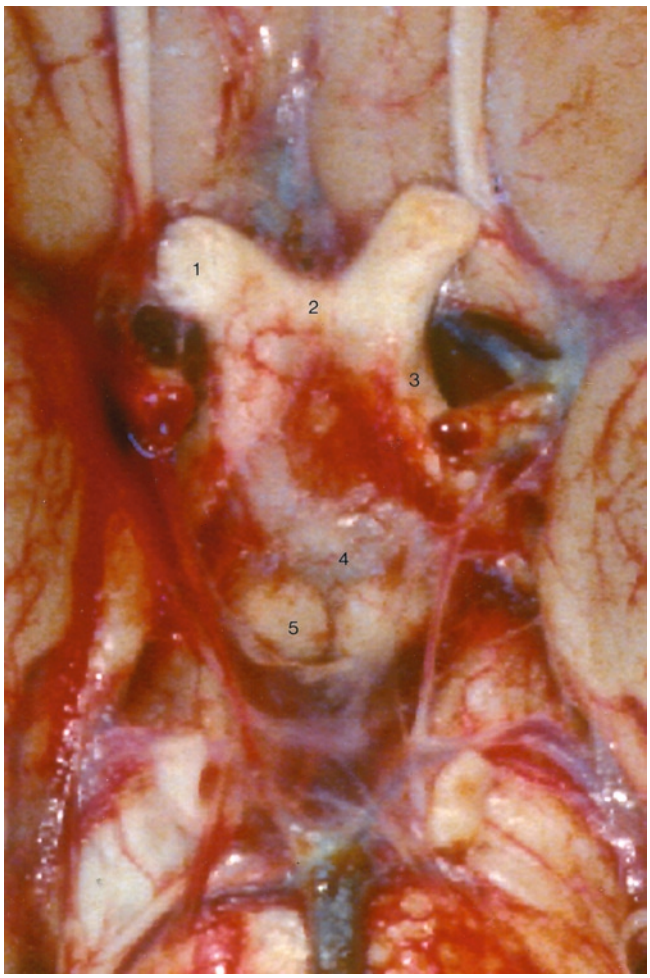


**Fig. 13.2** Basal view of the hypothalamus. The following structures are indicated by numbers: (1) optic nerve; (2) optic chiasm; (3) optic tract; (4) tuber cinereum; (5) mammillary body

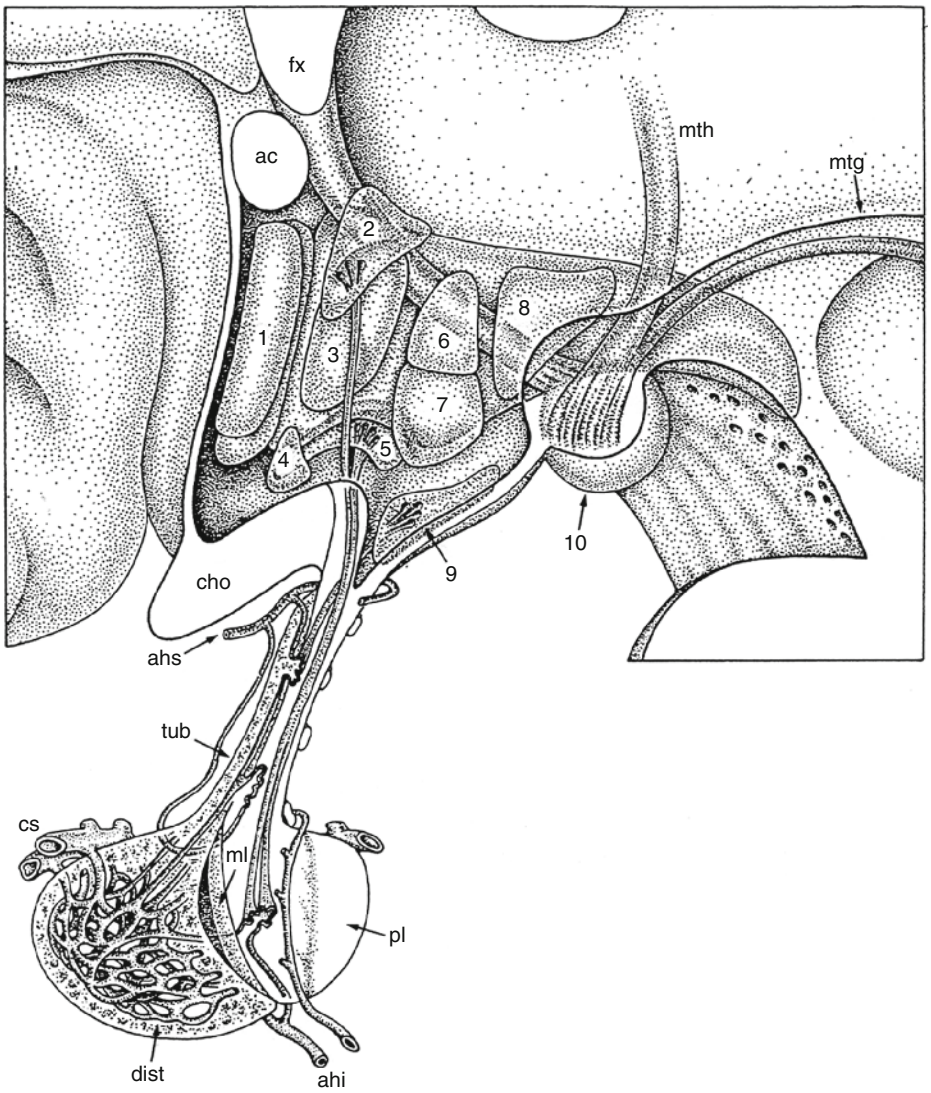


**Fig. 13.3** Overview of the human hypothalamus and the pituitary gland. *ac* anterior commissure, *ahi*, *ahs* inferior and superior hypophysial arteries, *cho* chiasma opticum, *cs* cavernous sinus, *dist* distal part of anterior pituitary lobe, *fx* fornix, *ml* middle pituitary lobe, *mtg* mammillotegmental tract, *mth* mammillothalamic tract, *pl* posterior pituitary lobe, *tub* tuberal part of anterior pituitary lobe, the following structures are indicated by numbers: (1) preoptic nucleus; (2) paraventricular nucleus; (3) anterior nucleus; (4) suprachiasmatic nucleus; (5) supraoptic nucleus; (6) dorsomedial nucleus; (7) ventromedial nucleus; (8) posterior nucleus; (9) arcuate or infundibular nucleus; (10) corpus mammillare (after Nauta and Haymaker 1969; from ten Donkelaar et al. 2006)

### 13.2.2 Hypothalamic Nuclei

The hypothalamic nuclei are usually divided into three groups, anterior, middle and posterior (Nauta and Haymaker 1969; Braak and Braak 1987, 1992; Swaab 1997, 2003; Koutcherov et al. 2002; Saper 2004). The **anterior group** includes the preoptic nuclei, the suprachiasmatic nucleus (SCN) and two magnocellular nuclei: the supraoptic nucleus and the paraventricular nucleus. The **middle group** includes the dorsomedial and ventromedial nuclei and the tuberal nuclei. The **posterior group** consists of the posterior hypothalamic area and the mammillary body.

The most prominent nuclei in the **chiasmatic region** are the supraoptic and paraventricular nuclei. The **supraoptic nucleus** covers the posterior part of the optic chiasm and the proximal part of the optic tract (Fig. 13.4). It consists of three parts: (1) a large dorsolateral part, which contains 53,000 neurons, 90% of which contain vasopressin and 10% oxytocin (Dierickx and Vandesande 1977; Fliers et al. 1985); (2) a dorsomedial part and (3) a ventromedial part. The latter parts together contain some 23,000 neurons; 85% of these contain vasopressin and 15% oxytocin (Dierickx and Vandesande 1977). The **paraventricular nucleus** forms an elongated plate of neurons close to the third ventricle and contains some 25,000 vasopressinergic neurons and 21,000 oxytocinergic neurons (Wierda et al. 1991; van der Woude et al. 1995). The vasopressinergic neurons are larger than the oxytocinergic cells (Dierickx and Vandesande 1979). The hormones are transported via the hypothalamohypophysial tract and released into blood vessels of both the infundibulum and the neurohypophysis (see Sect. 13.4). In patients in which a ***hypophysectomy*** was performed as palliative treatment of

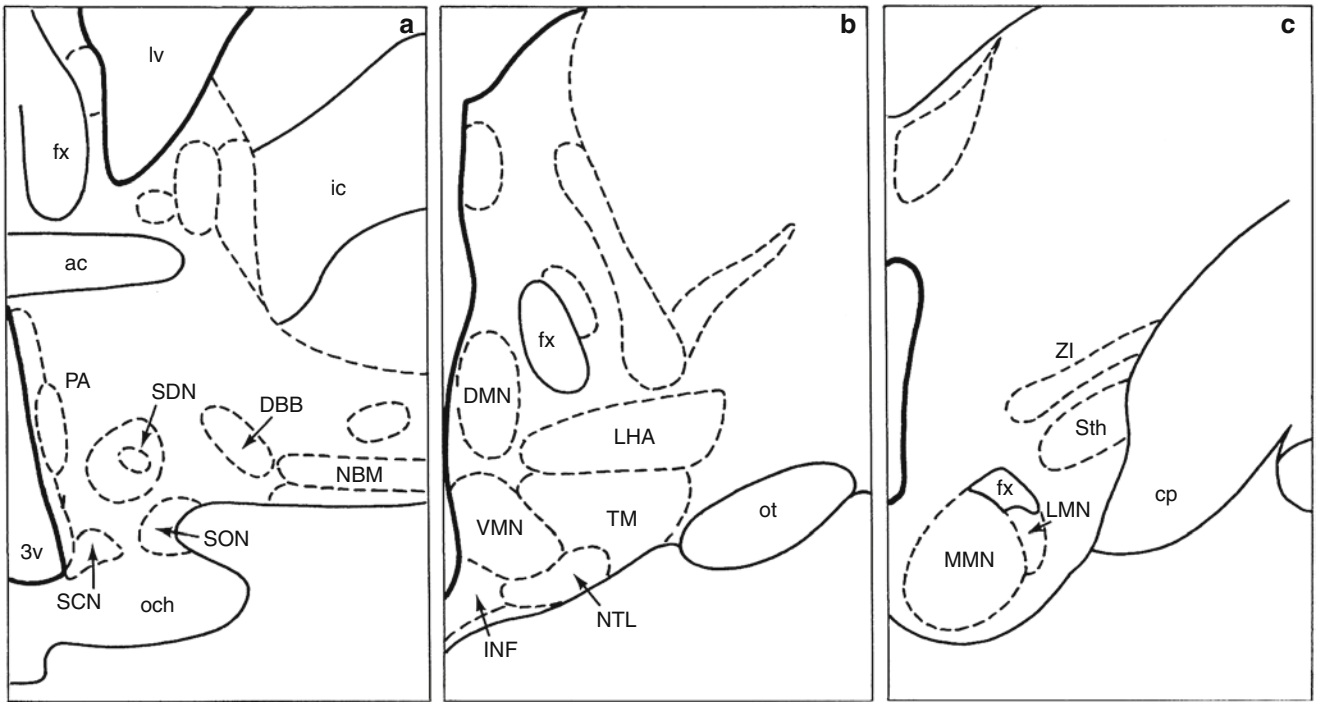


**Fig. 13.4** (**a**–**c**) Series of diagrams of the human hypothalamus. *ac* anterior commissure, *cp* cerebral peduncle, *DBB* (vertical) nucleus of diagonal band, *DMN* dorsomedial nucleus, *fx* fornix, *ic* internal capsule, *INF* infundibular (arcuate) nucleus, *LHA* lateral hypothalamic area, *lv* lateral ventricle, *LMN* lateromammillary nucleus, *MMN* medial mammillary nucleus, *NBM* nucleus basalis of Meynert, *NTL* nucleus tuberalis lateralis, *och* optic chiasm, *ot* optic tract, *PA* paraventricular nucleus, *SCH* suprachiasmatic nucleus, *SDN* sexually dimorphic nucleus of the preoptic area, *SON* supraoptic nucleus, *Sth* subthalamic nucleus, *TM* tuberomammillary nucleus, *VMN* ventromedial nucleus, *ZI* zona incerta, *3v* third ventricle (after Fernández-Guasti et al. 2000)

hormone-dependent metastatic mamma carcinoma, Morton (1969) found an average loss of supraoptic and paraventricular neurons of more than 80%. The neurons of the supraoptic and paraventricular nuclei form a population of extremely stable cells in normal ageing and Alzheimer disease (Swaab et al. 1993; Swaab 1997).

Halfway between the supraoptic and paraventricular nuclei the **sexually dimorphic intermediate nucleus** is found, first delineated by Brockhaus (1942) and later by Gorski et al. (1978). Swaab and co-workers showed that the volume of this small nucleus is considerably larger in men than in age-matched women (Swaab and Fliers 1985; Swaab and Hofman 1988; Férnandez-Guasti et al. 2000). Allen et al. (1989) described two other sexually dimorphic nuclei in the anterior hypothalamus (Fig. 13.5).

The periventricular zone of the preoptic area contains the periventricular preoptic nucleus, a marked lateral extension of the periventricular cell group, known as the uncinate nucleus, and the SCN. The SCN consists of small neurons that are almost devoid of basophilic material and pigment (Braak and Braak 1992). This nucleus receives a direct retinal projection (Moore 1973; Sadun et al. 1984; Dai et al. 1998). Its efferents influence the production of melatonin in the pineal gland. The nucleus is considered as an endogenous clock of the brain playing an important role in the control of biological rhythms (Moore 1982; Sadun et al. 1984; Swaab et al. 1985; Saper et al. 2005a). Lesions of the SCN result in loss of daily rhythms of wake–sleep activity, feeding, body temperature and a variety of hormones (Moore 1997; see Sect. 13.5). In rats, the SCN gives rise to three major output pathways (Swanson and Cowan 1975a; Watts and Swanson 1987; Watts et al. 1987): (1) a dorsal pathway to the medial preoptic area and the paraventricular nucleus; (2) a caudal pathway to the retrochiasmatic area and the capsule of the ventromedial hypothalamic nucleus and (3) to a column of tissue that arches upwards and backwards from the SCN and which includes the **subparaventricular zone** (**SPZ**) and the dorsomedial nucleus (DMN). This projection terminates in the ventral and dorsal parts of the SPZ and then continues to the DMN. Neurons within the dorsal SPZ are necessary for organizing circadian rhythms of body temperature, whereas neurons in the ventral SPZ are needed for circadian rhythms of sleep and waking (Saper et al. 2005a). Recently, the **ventrolateral preoptic nucleus** has been recognized as an important control centre for the regulation of sleep (Saper et al. 2005b; see Chap. 5).

A lesion in the suprachiasmatic region results in disturbed circadian rhythms in humans (Schwartz et al. 1986; Cohen

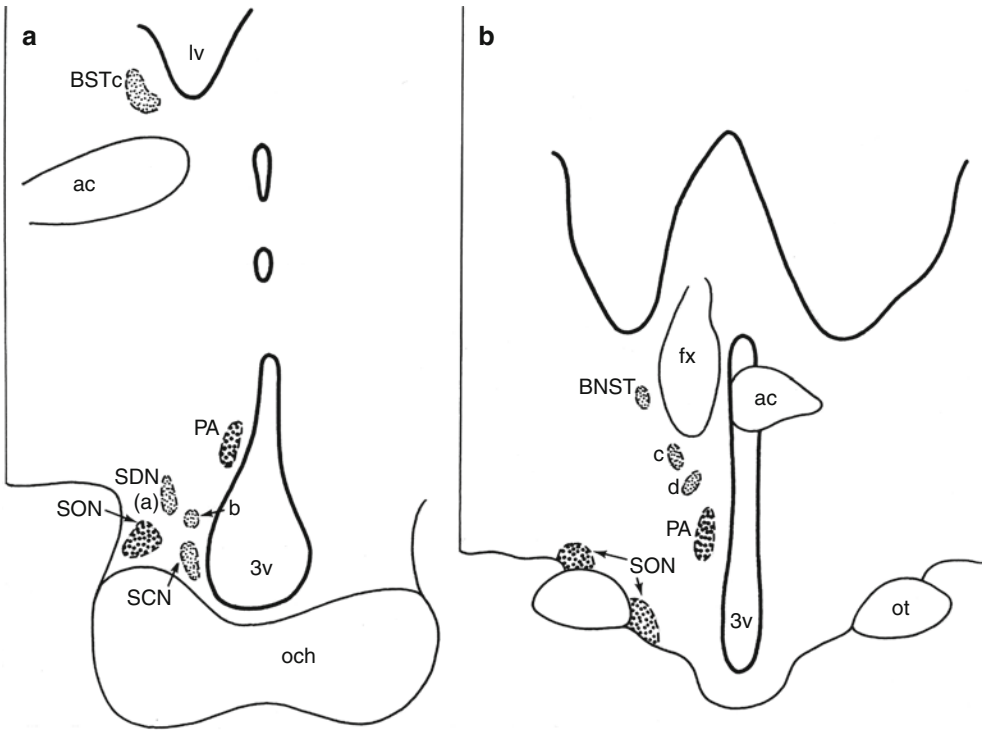


**Fig. 13.5** (**a**, **b**) Topography of the sexually dimorphic nuclei in the human hypothalamus. The anterior commissure (*ac*), the central nucleus of the bed nucleus of the stria terminalis (*BSTc*), the darkly staining component of the bed nucleus of the stria terminalis (*BNST*), the interstitial nuclei of the anterior hypothalamus (INAH) 2–4 (*b*, *c*, *d*), the suprachiasmatic nucleus (*SCN*) and the sexually dimorphic nucleus of the preoptic area (*SDN*) or INAH1 (*a*) vary according to sex. The suprachiasmatic nucleus, INAH3 and the anterior commissure are different in relation to sexual orientation. Other abbreviations: *fx* fornix, *lv* lateral ventricle, *PA* paraventricular nucleus, *och* optic chiasm, *ot* optic tract, *SON* supraoptic nucleus, *3v* third ventricle (after Swaab 2003)

and Albers 1991). Schwartz and co-workers described a 54-year-old postmenopausal woman with a discrete metastasis of a rectum adenocarcinoma in the ventral hypothalamus, the optic chiasm and the neurohypophysis who developed an abnormal daily temperature rhythm. The number of vasopressinergic neurons in the SCN was only 23% of the control values for the group of 50- to 80-year-old women (Swaab 1997). In Alzheimer disease, a remarkable cell loss is found in the SCN, causing disturbances in circadian rhythms (Swaab et al. 1985; Mirmiran et al. 1989; van de Nes et al. 1993).

The voluminous **ventromedial nucleus** (**VMN**) is a conspicuous structure in the **tuberal region** (Fig. 13.4). The cell density is higher at its periphery than in the centre of the nucleus. The VMN has extensive connections with many neighbouring structures and major projections to the magnocellular nuclei of the basal forebrain (Jones et al. 1976; Krieger et al. 1979). In rats, the VMN is presumed to play a role in various sexually dimorphic functions such as female mating behaviour, gonadotropin secretion, feeding and aggression (see Swaab 2003). Positron emission tomography (PET) studies have indicated that the human VMN may be involved in reactions to pheromones in a sexually dimorphic way. In contrast to men, women smelling an androgen-like pheromone activate this region (Savic et al. 2001). The VMN may be involved in eating behaviour and metabolism. Tumours in this area cause symptoms such as hyperphagia, episodic rage, emotional lability and intellectual deterioration (Reeves and Plum 1969; see ***Clinical case 13.1***).

The DMN is poorly differentiated in the human brain (Braak and Braak 1992) and covers the rostral and dorsal poles of the VMN. In rats, the nucleus is the final common output site for a wide range of circadian rhythms (Saper et al. 2005a). It projects to the ventrolateral preoptic nucleus, the lateral hypothalamic area (LHA) and the paraventricular nucleus (Thompson et al. 1996) and, therefore, has extensive outputs to the major effector sites for circadian rhythms of sleep and waking, locomotor activity, feeding and corticosteroid production. Periventricular and infundibular nuclei are found medial to the VMN. The **infundibular** or **arcuate nucleus** contains, among many other neuropeptides and transmitters, gonadotropin-releasing hormone (GnRH) neurons, earlier known as luteinizing hormone-releasing hormone (LHRH) neurons (Muske 1993; Swaab 1997, 2003). GnRH neurons are found in the human foetal hypothalamus from the ninth week of development. The GnRH neurons are generated in the epithelium of the medial olfactory pit and migrate from the nose into the forebrain along the branches of the terminal and vomeronasal nerves (Schwanzel-Fukuda and Pfaff 1989; Schwanzel-Fukuda et al. 1989, 1996; ten Donkelaar et al. 2006). Observations in ***Kallmann syndrome*** suggest that GnRH neurons fail to migrate from the olfactory placode into the developing brain.

The basolateral part of the tuberal region contains the lateral tuberal and tuberomammillary nuclei. The large **lateral tuberal nucleus** shows a pronounced cell loss in Huntington disease (Kremer et al. 1990). The **tuberomammillary nucleus**

**(TMN)** surrounds the lateral tuberal nucleus and extends through the posterior tuberal and anterior mammillary regions. It contains histaminergic neurons (Takeda et al. 1984; Lin et al. 1988, 1994; Panula et al. 1990; Lin 2000; Haas and Panula 2003).

The LHA contains several populations of neurons that contribute to the regulation of wakefulness (Saper et al. 2005b). A **perifornical group** producing **orexin** projects to the cerebral cortex and the basal forebrain as well as to the brain stem arousal system (Peyron et al. 1998; see Chap. 5). These neurons are active during wakefulness. Another population of LHA neurons contain melanin-concentrating hormone (MCH). These have similar projections but are most active during rapid eye movement (REM) sleep.

The **mammillary body** is the most conspicuous component of the medial hypothalamus at the posterior level. In humans, the medial portion of the **medial mammillary nucleus** reaches prodigious proportions, causing the bulging shape in the floor of the hypothalamus. The lateral part of the medial mammillary nucleus is much smaller and often split off from the lateral border of the medial subnucleus by a sheet of fornix fibres. Although the neurons in the lateral part of the medial mammillary nucleus are identical in size, shape and staining characteristics to those in the medial part of the nucleus, Gagel (1928), Grünthal (1933) and Le Gros Clark (1936, 1938) called this the "lateral mammillary nucleus". This suggested homology to the lateral mammillary nucleus of rodents, in which the lateral mammillary neurons are much larger and more darkly stained. Saper (2004) described a collection of larger, more densely staining neurons located along the lateral edge of the medial mammillary nucleus as the **lateral mammillary nucleus**.

**Clinical Case 13.1 Ventromedial Hypothalamus Syndrome**

Tumours of the hypothalamus most often present by compression of the adjacent optic chiasm or optic tract. In rare cases, endocrine, autonomic and behavioural signs predominate as described by Reeves and Plum (1969). Following invasion of a tumour into the area of the ventromedial hypothalamic nuclei, they described (see **Case report**): (1) episodic rage; (2) emotional lability; (3) hyperphagia with obesity and (4) intellectual deterioration. Memory loss is the most prominent feature of intellectual decline. Although lesions of the fornix and the mammillary bodies may be important in this respect, a primary role for the VMN in memory has been postulated (Reeves and Plum 1969; Flynn et al. 1988).

**Case report:** Reeves and Plum's case of a hypothalamic tumour in a 22-year-old female, which affected the ventromedial hypothalamic nuclei and the median eminence bilaterally (Fig. 13.6), clearly illustrates the key role of the hypothalamus in mediating endocrine, autonomic and behavioural functions. The patient showed loss of: (1) control of eating with hyperphagic obesity; (2) water and salt balance with DI; (3) endocrine metabolism with hypoadrenalism, hypogonadism and hypothyroidism and (4) temperature regulation with episodic fever. Moreover, attacks of rage and loss of mental functions point to the importance of the hypothalamus and its converging pathways in integrating emotional and cognitive functions with behaviour and control of systemic physiology.

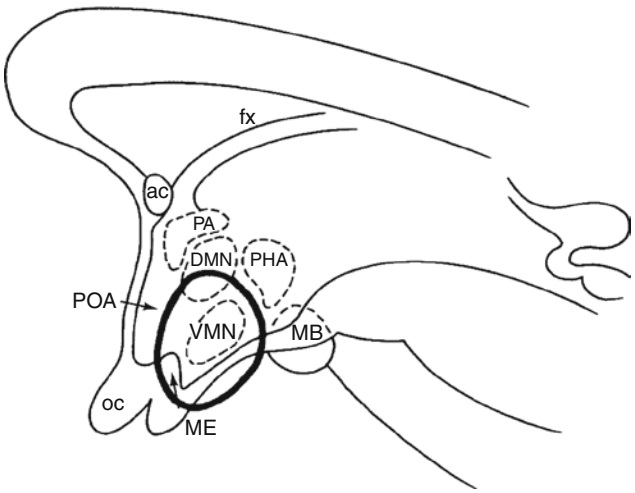


**Fig. 13.6** Sagittal section of the hypothalamus showing the extent of the tumour in the ventromedial hypothalamus syndrome as reported by Reeves and Plum (1969). *ac* anterior commissure, *DMN* dorsomedial nucleus, *fx* fornix, *LHA* lateral hypothalamic area, *MB* mammillary body, *ME* median eminence, *oc* optic chiasm, *PHA* posterior hypothalamic area, *PA* paraventricular nucleus, *POA* preoptic area, *VMN* ventromedial nucleus (after Reeves and Plum 1969)

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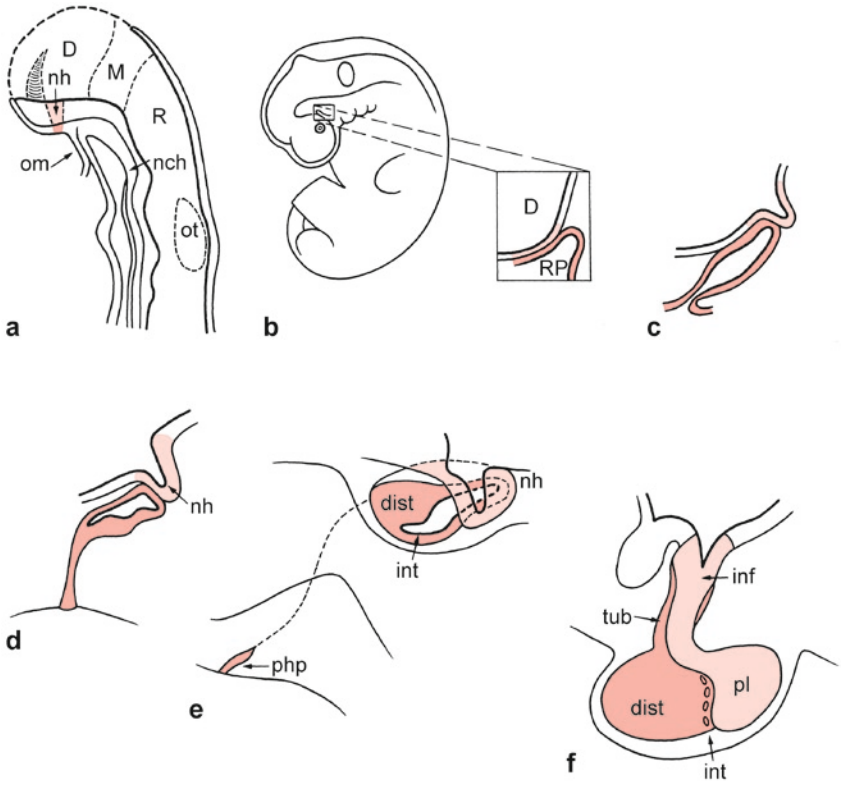


**Fig. 13.7** Development of the human pituitary gland: (**a**) median section at 4.5 weeks of development (Carnegie stage 11); (**b**) embryo of 4.5 weeks of development (stage 14), showing Rathke's pouch; (**c**) at 6 weeks (stage 17); (**d**) at stage 19, (**e**) at the end of the embryonic period (stage 23), (**f**) foetal pituitary. The developing neurohypophysis (*nh*) is indicated in *light red* and the adenohypophysis in *red*. *D* diencephalon, *dist* distal part, *inf* infundibulum, *int* intermediate part, *M* mesencephalon, *nch* notochord, *om* oral membrane, *ot* otocyst, *php* pharyngeal pituitary, *pl* posterior lobe, *R* rhombencephalon, *RP* Rathke's pouch, *tub* tuberal part (after O'Rahilly and Müller 2001; from ten Donkelaar et al. 2006)

### 13.2.3 The Pituitary Gland

The pituitary gland consists of two main parts, the adenohypophysis and the neurohypophysis that form the sellar pituitary. The two components are in close contact from the beginning of development (Fig. 13.7). The **adenohypophysial primordium** is induced by the adjacent floor of the rostral forebrain, from which the neurohypophysis develops (Sheng and Westphal 1999; O'Rahilly and Müller 2001; ten Donkelaar et al. 2006). In human embryos, the primordium of the adenohypophysis is situated immediately rostral to the oropharyngeal membrane and forms the adenohypophysial pouch of Rathke. The floor of the forebrain forms the **neurohypophysial evagination** and, before the end of the embryonic period, the pouch loses its contact with the roof of the mouth. The portion of the pouch that is in contact with the neurohypophysial evagination forms the **pars intermedia** of the hypophysis. Other parts of the adenohypophysis that surround the stalk of the neurohypophysis form the **pars tuberalis** and the remaining part forms the **pars distalis**. The oropharyngeal part remains as the **pharyngeal hypophysis** throughout life. Pituitary hormones are produced at the end of the embryonic period (Asa et al. 1986, 1988; Ikeda et al. 1988; Hori et al. 1999b). The anterior part of the pituitary gland may remain continous with the pharyngeal roof through a **persistent craniopharyngeal canal** as a **pharyngosellar pituitary** (Hori et al. 1995, 1999a; ten Donkelaar et al. 2006; see ***Clinical case 13.2***). Remnants of Rathke's pouch may give rise to ***craniopharyngioma*** (see ***Clinical case 13.3***).

### Clinical Case 13.2 Persistent Craniopharyngeal Canal with Pharyngosellar Pituitary

In ***pharyngosellar pituitary***, the anterior part of the gland is continuous from the pharyngeal roof to the sella turcica. Hori et al. (1995) described this rare malformation in a 17-gestational-week-old male foetus with an encephalocele and amnion rupture sequence (see **Case report**). This anomaly has been found in several cases of trisomy 18 (Kjaer et al. 1998).

**Case report:** The pregnancy of a 27-year-old mother was unremarkable until at gestational week 17 the amnion was ruptured and the foetus was aborted spontaneously. Examination of the foetus revealed multiple malformations of the face and a large and a smaller encephalocele covered with skin in the vertex of the microcephalic head. After removing the covering of the head, a large round skull defect was found through which the larger encephalocele herniated. The skull base was hypoplastic: the anterior cranial fossa was narrow in transverse diameter, the middle fossa was shallow and the posterior fossa was normal in size. Anterior and posterior protuberances of the sella were absent. The pituitary gland was found in the ordinary position when observed from the cranial base. Part of the skull base, including the sella turcica, the clivus and the pharyngeal roof, was removed and divided through the midline (Fig. 13.8a); both blocks were embedded in paraffin without decalcification and sliced serially. Sections were stained by haematoxylin and eosin, periodic acid-Schiff (PAS) stain and Gomori's reticulin staining. Immunostaining for pituitary hormones was also performed.

The pituitary gland was found in the **persistent craniopharyngeal canal** as an elongated structure expanding from the pharyngeal roof to the sella turcica (Fig. 13.8b), forming a **pharyngosellar pituitary**. The pituitary tissue was covered with a poorly ciliated epithelial layer at its pharyngeal end. The pituitary stalk and the posterior lobe were histologically normal. Immunohistochemical examination for anterior pituitary hormones showed that the distribution of hormone-producing cells in the malformed pituitary tissue was irregular: thyrotropic hormone (TSH) producing, follicle-stimulating hormone (FSH) producing and luteinizing hormone (LH) producing cells were nearly absent in the sellar and middle sections of the pituitary but were found in small numbers in its pharyngeal part. Somatotropic hormone (STH) producing, prolactin-releasing hormone (PRL) producing and adrenocorticotropic hormone (ACTH) producing cells were distributed diffusely. ACTH-producing cells were abundant in the pharyngeal part.

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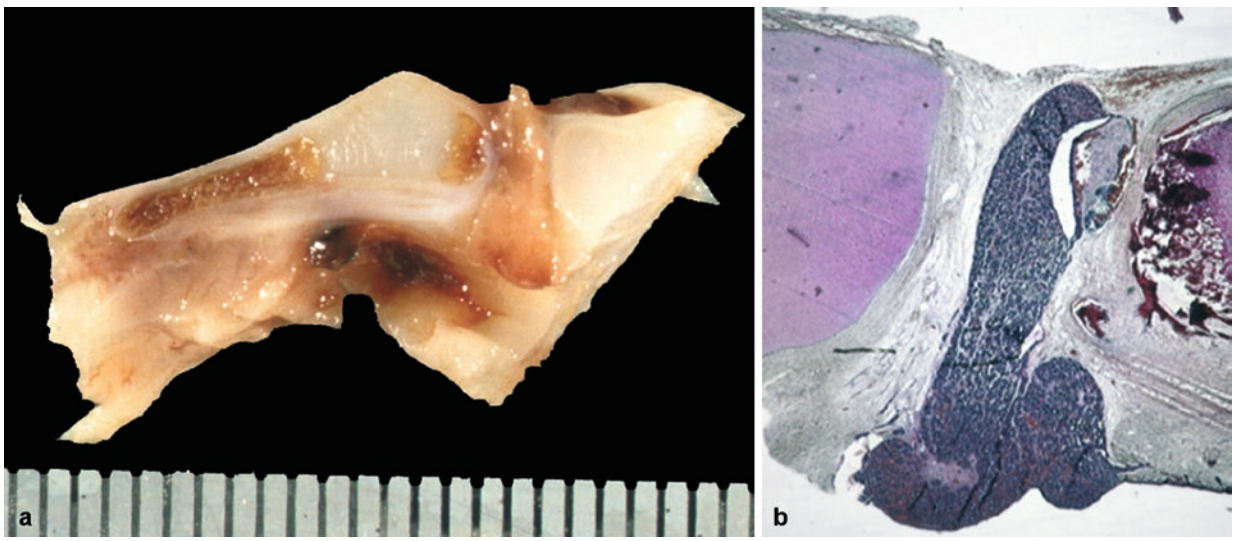


**Fig. 13.8** Pharyngosellar pituitary: (**a**) gross appearance of the pituitary gland in the craniopharyngeal canal; (**b**) Gomori-stained section, showing the pharyngeal pituitary attached to the posterior lobe (from Hori et al. 1995; with permission from Springer)

**Clinical Case 13.3 Craniopharyngioma**

A low-grade developmental neoplasm, ***craniopharyngioma***, is thought to be derived from squamous cell nests, thought to be vestigial remnants of Rathke's pouch, the pituitary anlage, and can arise anywhere along the craniopharyngeal canal (Costin 1979; Chong and Newton 1993). Rare cases have been described with a persistent craniofacial canal (Chen 2001) or with a nasopharyngeal extension of a normally functioning pituitary gland extending into the nasopharynx (Ekinci et al. 2002).

**Case report:** A 21-year-old male patient presented with weight increase, gynaecomasty and visual loss reminiscent of a suprasellar process. An MRI showed a large suprasellar process (Fig. 13.9a), which was removed neurosurgically. Neuropathological examination revealed a craniopharyngioma of the adamantinomatous type (Fig. 13.9b).

This case was kindly supplied by Pieter Wesseling (Department of Pathology, Radboud University Nijmegen Medical Centre).

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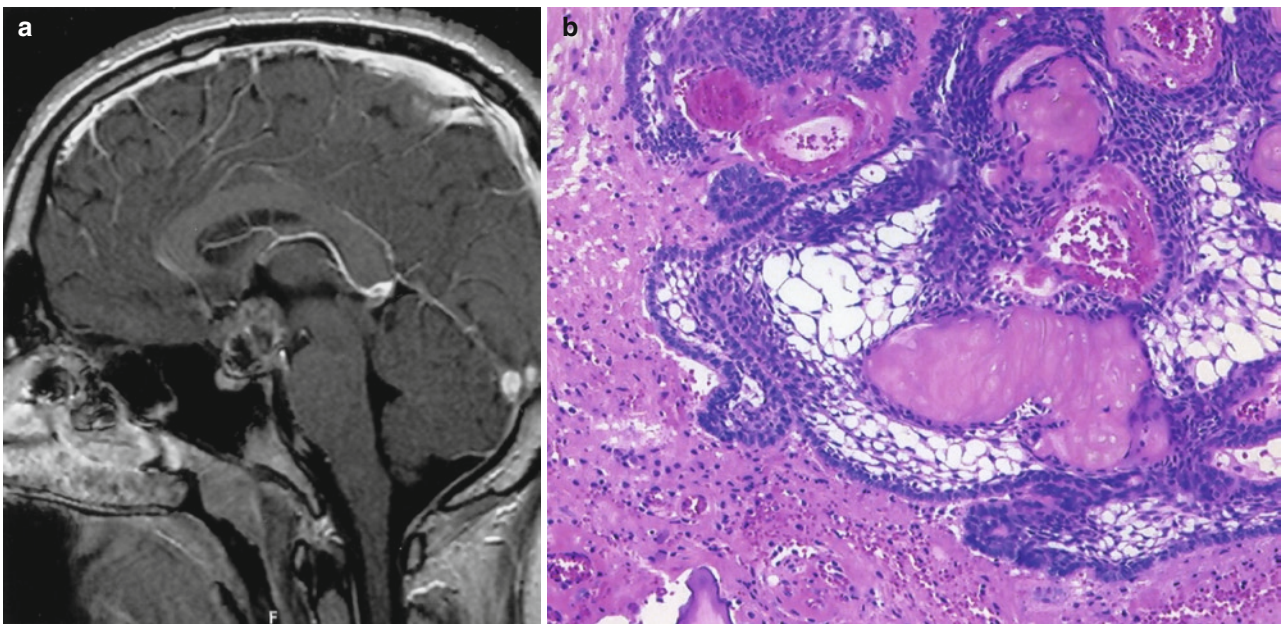



**Fig. 13.9** (**a**) Sagittal MRI of a suprasellar tumour that appeared to be a craniopharyngioma; (**b**) microscopic section showing the adamantinomatous subtype of a craniopharyngioma (courtesy Pieter Wesseling, Nijmegen)

### 13.2.4 Circumventricular Organs

The CVOs are located around or in relation to the ventricular system and several of them are closely related to the hypothalamus. The CVOs are highly vascularized structures without a blood–brain barrier and provide for the exchange of substances between the blood and the brain (Broadwell and Brightman 1976; McKinley et al. 2004) and include the subfornical organ, the vascular organ of the lamina terminalis, the pineal gland, the median eminence, the neurohypophysis and the area postrema. The human **organon vasculosum laminae terminalis** (**OVLT**) or vascular organ of the lamina terminalis is at its greatest extent in the lamina terminalis, approximately midway between the optic chiasm and the anterior commissure (Duvernoy et al. 1969). The OVLT appears to be part of a neural network within the lamina terminalis and hypothalamus, which is involved in the regulation of fluid balance (McKinley

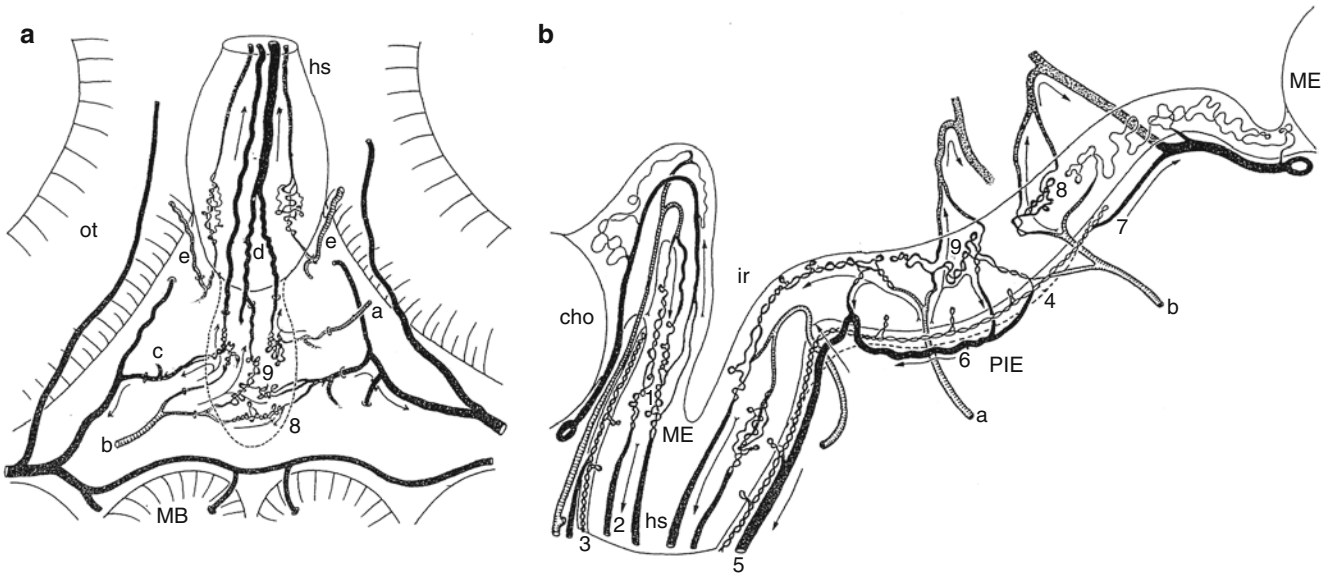



**Fig. 13.10** The human circumventricular organs: (**a**) vascularization of the floor of the diencephalon; (**b**) median section of the floor of the third ventricle. In **a**, only the deep network is shown. *a* and *b* supply the postinfundibular eminence (*PIE*) or posterior tuber; one deep network (*8*) is exclusively drained by tuberal veins (*c*), another deep capillary network (*9*) has mixed drainage via lateral tuberal veins (*c*) and via long posterior portal vessels (*d*); a branch of the superior hypophysial artery (*e*) reaches the deep network of the median eminence (*ME*); in **b**, vascular tuberohypophysial connections are shown: (1) capillary tufts belonging to the deep network of the primary plexus supplied by tuberal arterioles; (2) portal vessels; (3) surface network and its drainage; (4) superficial network and its drainage; (5, 6) portal vessels; (7) drainage of the surface network by a tuberal vein; (8) deep network exclusively drained by tuberal veins (*arrows*); (9) deep network with mixed drainage towards the hypophysis. Other *abbreviations*: *cho* chiasma opticum, *hs* hypophysial stalk, *ir* infundibular recess of third ventricle, *MB* mammillary body, *ot* optic tract (after Duvernoy 1972)

et al. 1984, 2004). The **pineal gland** or **epiphysis cerebri** has an ovoid shape. Its stalk lines the pineal recess, whose superior lip links the pineal gland to the habenular region and its inferior lip to the posterior commissure (Duvernoy et al. 2000). The pineal gland is a key structure of the circadian system and is connected to the SCN. It contains pinealocytes, which produce **melatonin**, and astrocytes. The pineal gland is innervated by a multiple pathway from the SCN to the paraventricular nucleus, which in its turn innervates the upper thoracic intermediolateral cell column. From here, sympathetic fibres go to the superior cervical ganglion that sends noradrenergic fibres to the pineal gland (Ariëns Kappers 1965; Duvernoy et al. 2000). Under the influence of the noradrenergic innervation, melatonin is produced and released causing circadian fluctuations in many brain functions.

The **median eminence** with its specialized vascular arrangement and vascular links to the anterior pituitary is the site of neurosecretion of a number of releasing hormones synthesized in the hypothalamus and the preoptic region. It regulates the secretions of the anterior pituitary. **Oxytocin** and **vasopressin** are synthesized in the magnocellular neurons of the paraventricular and supraoptic nuclei and reach the most distal part of the infundibular process (the pars nervosa or posterior pituitary) via axonal transport through the infundibulum (Haymaker 1969; Daniel and Pritchard 1975; Page 1986). In non-primate mammals, the median eminence forms the midline tissue immediately caudal to the optic chiasm that connects to the pituitary stalk. In the human hypothalamus, the median eminence becomes incorporated into the upper part of infundibular stem (Duvernoy 1972; Daniel and Pritchard 1975; Fig. 13.10). The most striking feature of the median eminence and the neurohypophysis is the specialized configuration of its vascular arrangement. The blood supply to these regions comes from the superior hypophysial and inferior hypophysial arteries (Xuereb et al. 1954a, b; Duvernoy 1972; Figs. 13.3 and 13.10). Branches of the suprahypophysial artery descend within the tuberal part along the rostral and lateral surfaces of the infundibulum and give rise to arterioles which enter the infundibulum. These bend upward towards the median eminence to form complex capillary loops in both the superficial and the deeper parts of the infundibulum. These capillary arrangements form the primary capillary complex of the median eminence in the upper infundibular stem. The continuation of these capillary coils gives rise to the **long portal vessels**, which deliver blood to the pars distalis. These portal veins travel down the surface (pars tuberalis) and inferior of the infundibulum to supply the sinusoids of the pars distalis (Xuereb et al. 1954a, b; Duvernoy 1972).

## 13.3 Fibre Connections

The myelinated hypothalamic fibre tracts such as the fornix, the mammillothalamic tract and the stria terminalis can easily be identified in fibre-stained sections. Several other hypothalamic fibre systems such as the medial forebrain bundle (MFB) and the dorsal longitudinal fascicle of Schütz are composed mainly of thin fibres. The hypothalamus is reciprocally connected to a large number of forebrain areas including the extended amygdala, the ventral striatum, the septum, the hippocampus, many cortical areas, the cerebellum, the brain stem and the spinal cord. The efferent connections from the medial preoptic and LHAs are primarily short and confined to nearby hypothalamic cell groups (Saper et al. 1978, 1979). The VMN in monkeys has somewhat more extensive projections, running along the MFB and reaching rostrally into the bed nucleus of the stria terminalis, laterally into the basal nucleus of Meynert and the area surrounding the central nucleus of the amygdala and caudally into the midbrain reticular formation and central grey (Jones et al. 1976; Saper et al. 1976b, 1979). The projections of the posterior hypothalamic area are primarily through the periventricular grey matter of the hypothalamus and thalamus and into the midbrain central grey (Veazey et al. 1982). The afferent and efferent fibre connections of the hypothalamus are summarized in Fig. 13.11a, b, respectively.

**Hypothalamic afferents** include fibres originating from the following structures (Fig. 13.11a):

1. Somatosensory structures in the spinal cord (layers I, V and X of the spinal grey; Burstein et al. 1987, 1996; Newman et al. 1996) and the caudal part of the spinal trigeminal nucleus (Burstein 1996).
2. Viscerosensory structures such as the nucleus of the solitary tract (Ricardo and Koh 1978; Ciriello and Calaresu 1980a, b), the ventrolateral superficial reticular area in the ventrolateral medulla (Ciriello and Caverson 1984), and the parabrachial nuclei (Fulwiler and Saper 1984; Pritchard et al. 2000).
3. The noradrenergic cell groups A1, A2, A5, A6 (the locus coeruleus) and A7, the adrenergic cell groups C1 and C2, and the serotonergic dorsal raphe and central superior nuclei (see Chap. 5).
4. The periaqueductal grey (Mantyh 1983).
5. The deep cerebellar nuclei (Dietrichs and Haines 1989).
6. The subiculum (Swanson and Cowan 1977; see Chap. 14).

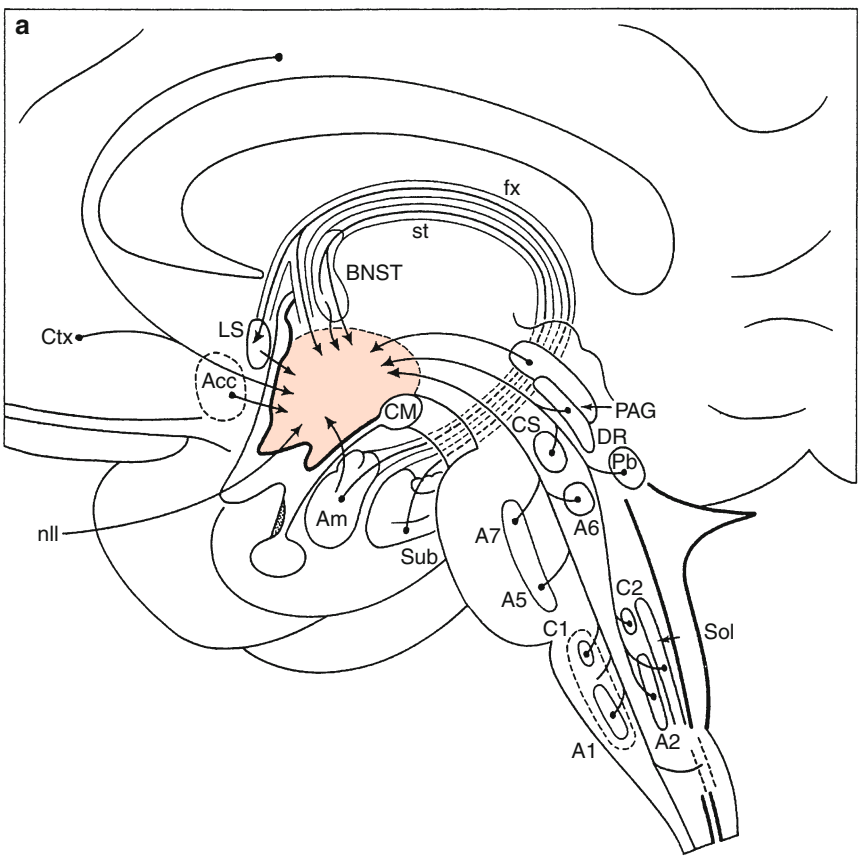
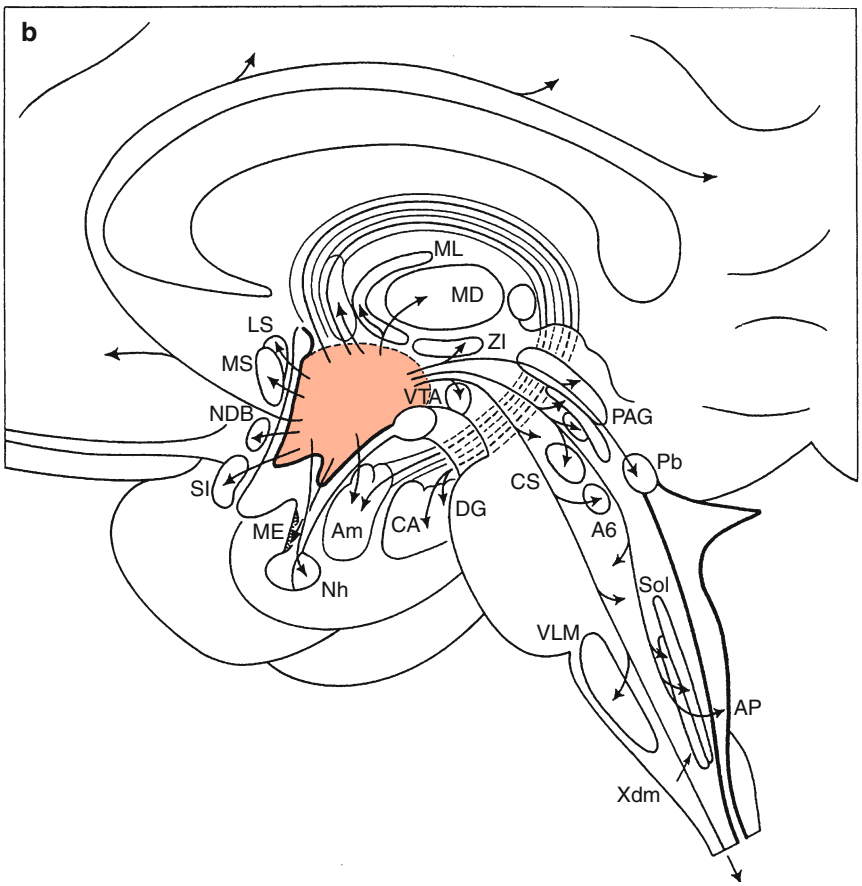



**Fig. 13.11** Summary of (**a**) the afferent and (**b**) the efferent connections of the hypothalamus. *A1–A7* noradrenergic cell groups, *Acc* nucleus accumbens, *Am* amygdala, *AP* area postrema, *BNST* bed nucleus of the stria terminalis, *CA* cornu Ammonis, *C1*, *C2* adrenergic cell groups, *CM* corpus mammillare, *CS* central superior nucleus, *Ctx* cortex cerebri, *DG* dentate gyrus, *DR* dorsal raphe nucleus, *fx* fornix, *LS* lateral septal nucleus, *MD* mediodorsal thalamic nucleus, *ME* median eminence, *ML* midline nuclei, *MS* medial septal nucleus, *NDB* nucleus of the diagonal band, *Nh* neurohypophysis, *nII* optic nerve, *PAG* periaqueductal grey, *Pb* parabrachial nucleus, *SI* substantia innominata, *Sol* nucleus of the solitary tract, *st* stria terminalis, *Sub* subiculum, *VLM* ventrolateral medulla, *VTA* ventral tegmental area, *Xdm* dorsal motor nucleus of vagus nerve, *ZI* zona incerta (after Nieuwenhuys et al. 2007)

**Fig. 13.11** (continued)




7. The septum (Swanson and Cowan 1979).
8. Various parts of the neocortex, including the prefrontal and cingulate cortices (Nauta and Haymaker 1969).
9. The olfactory bulb (Veazey et al. 1982; Smithson et al. 1989; Price et al. 1991).
10. The subfornical organ and the vascular organ of the lamina terminalis (McKinley et al. 2004).
11. Direct retinal projections to the SCN (Moore 1973; Sadun et al. 1984; Dai et al. 1998).
12. The amygdala via the stria terminalis and the ventral amygdalofugal pathway (see Chap. 14).
13. The bed nucleus of the stria terminalis (Swanson and Cowan 1979).

**Hypothalamic efferents** project to the following structures (Fig. 13.11b):

1. Various parts of the neocortex (see Sect. 13.3.4).
2. The septum (Veening et al. 1987).
3. The hippocampus (Haglund et al. 1984; Wyss et al. 1979; see Chap. 14).
4. The amygdala via both the stria terminalis and the ventral amygdalofugal pathway (see Chap. 14).
5. The anterior thalamic nuclei (see Sect. 13.3.2).
6. Thalamic midline nuclei (Canteras et al. 1994; Risold et al. 1994).
7. Via the stria medullaris to the habenular complex (Herkenham and Nauta 1977, 1979).
8. The zona incerta (Canteras et al. 1994).
9. Via the dorsal longitudinal fascicle of Schütz to the periaqueductal grey, the parabrachial nuclei, the locus coeruleus, the nucleus of the solitary tract and the area postrema (Beitz 1982; Veening et al. 1987; Roeling et al. 1994).
10. Via the MFB to the ventral tegmental area, the mesencephalic and rhombencephalic raphe nuclei, the mesencephalic reticular formation, the mesencephalic locomotor region, the lateral tegmental field, the ambiguus nucleus, the ventrolateral medulla, the marginal zone (layer I), the central grey and the intermediolateral nucleus of the spinal cord (Swanson et al. 1984, 1987; Luiten et al. 1985, 1987; ter Horst 1986; Holstege 1987; see Fig. 13.18).
11. The cerebellum (Dietrichs and Haines 1989; Dietrichs et al. 1992).
12. The pituitary gland (see Sect. 13.4).

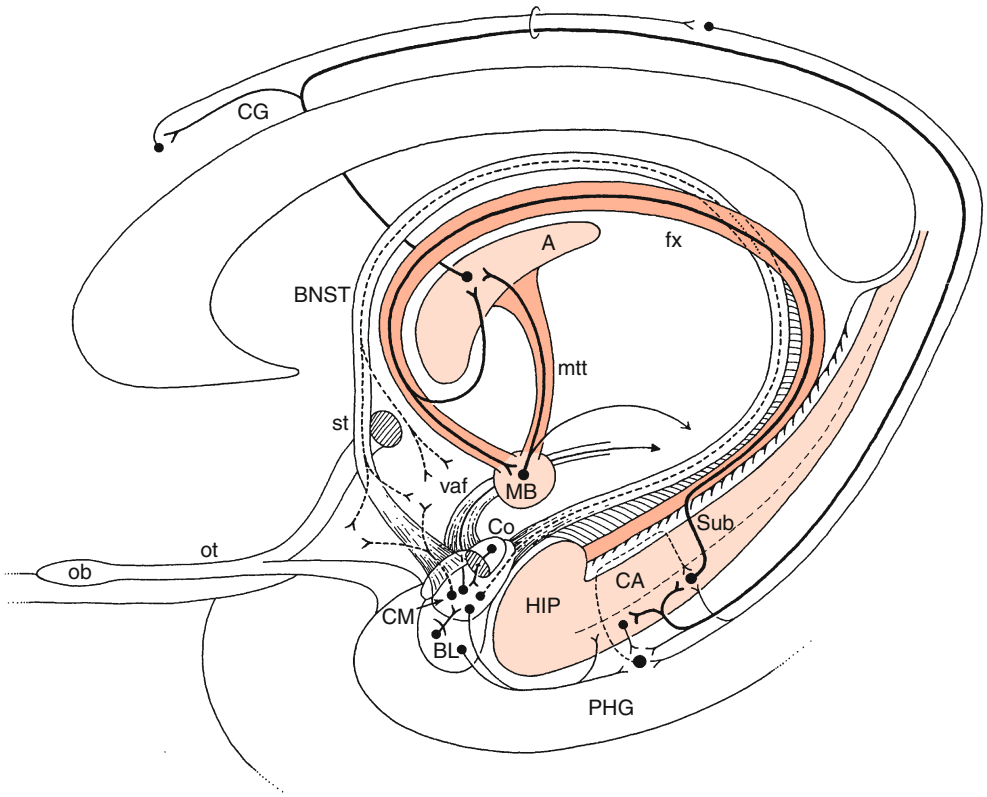



**Fig. 13.12** The human fornix. The hippocampus is indicated in *light red* and the fornix in *red*. *A* anterior thalamic nucleus, *BL* basolateral amygdaloid nucleus, *BNST* bed nucleus of the stria terminalis, *CA* cornu Ammonis, *CG* cingulate gyrus, *CM* centromedian amygdala, *Co* cortical amygdaloid nucleus, *HIP* hippocampus, *MB* mammillary body, *mtt* mammillothalamic tract, *ob* olfactory bulb, *ot* olfactory tract, *PHG* parahippocampal gyrus, *st* stria terminalis, *Sub* subiculum, *vaf* ventral amygdalofugal fascicle (after ten Donkelaar et al. 2007)

### 13.3.1 The Fornix

The **fornix** is a large fibre bundle (Fig. 13.12) that connects the hippocampal formation with the septal area (the **precommissural fornix**), the anterior thalamus and the hypothalamus (the **postcommissural fornix**). The subicular complex, rather than the hippocampus proper, is the origin of the postcommissural fornix (Swanson and Cowan 1975b). This fibre bundle arises mainly in the presubiculum and innervates the anteromedial, anteroventral and laterodorsal thalamic nuclei (Saunders et al. 2005). Fibres from both the subiculum and the presubiculum innervate the mammillary complex (Raisman et al. 1966; Meibach and Siegel 1975; Swanson and Cowan 1975b, 1977; Irle and Markowitsch 1982). Throughout its course through the hypothalamus, it innervates medial and lateral structures. Large lesions of the hippocampus and fornix result in anterograde transneuronal atrophy of the mammillary body (see ***Clinical case 13.4***).

**Clinical Case 13.4 Anterograde Transneuronal Atrophy of the Mammillary Body Following a Hippocampus Infarction**

**Case report:** A 60-year-old male died of pneumonia. Except for a left-sided infarction in the territory of the posterior cerebral artery (PCA) several years before, no other details were known. At autopsy, softening of the cerebral cortex of the left mediobasal occipital region was observed (Fig. 13.13a) and the left PCA showed severe atherosclerosis in contrast to the right one. The left mammillary body was atrophic (Fig. 13.13a). In frontal cut slices of the brain, unilateral atrophy of the left mammillary body and of the left fornix were found (Fig. 13.13b). Moreover, cystic infarction with total destruction of the posterior hippocampus including the subiculum was found (Fig. 13.13c).

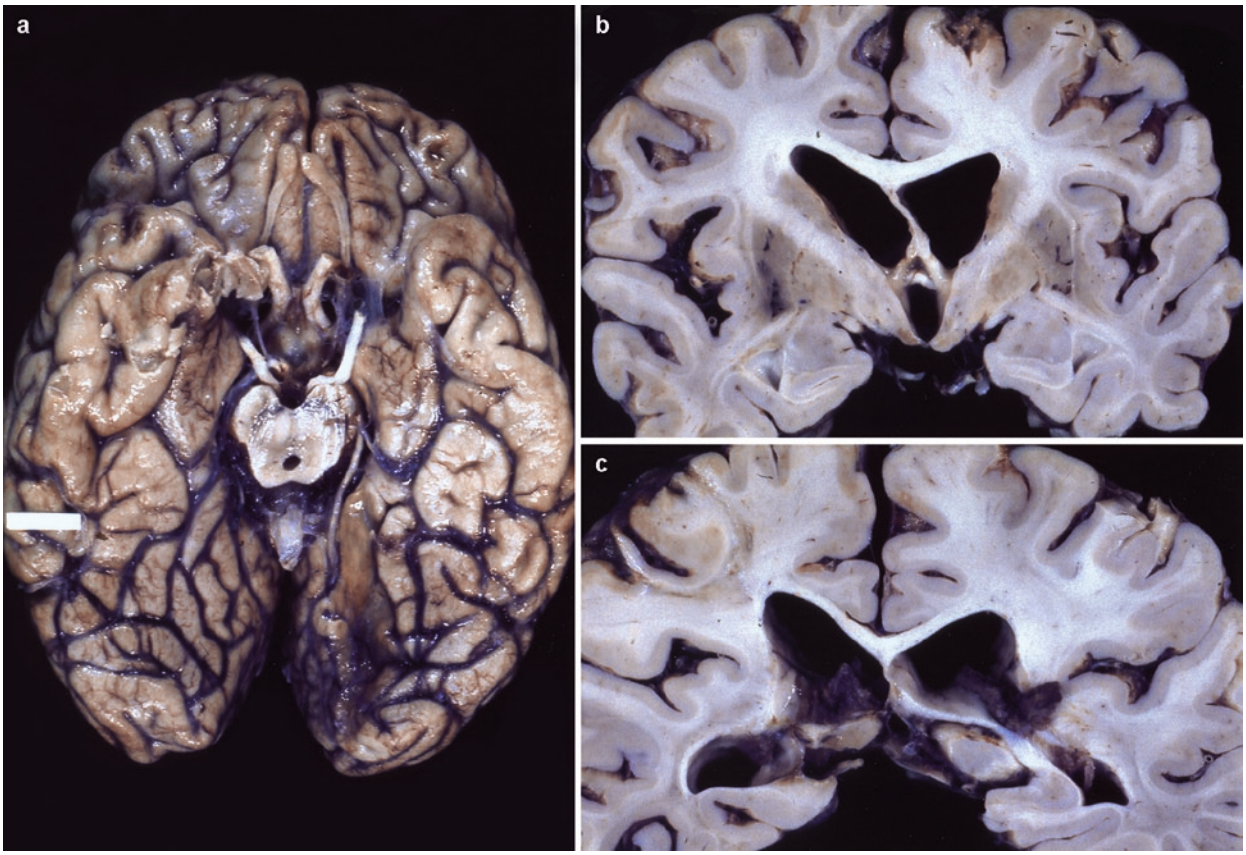



**Fig. 13.13** Left-sided infarction in the territory of the posterior cerebral artery (**a**, **c**) and the resulting anterograde transneuronal degeneration of the left mammillary body (**b**; see text for further explanation; courtesy Akira Hori, Toyohashi)

### 13.3.2 The Mammillothalamic Tract and the Mammillary Peduncle

The mammillary body stands out from the rest of the hypothalamus as it is not as closely related to autonomic and endocrine functions as the other parts of the hypothalamus. The efferent fibres of the mammillary body form the **principal mammillary fascicle** that passes dorsally and splits up into two components (Fig. 13.3): (1) the **mammillothalamic tract** of **Vicq d'Azyr**, which passes via the internal medullary lamina of the thalamus to the anterior thalamic nuclei; following a thalamic lesion including the mammillothalamic tract of Vicq d'Azyr, the mammillary body retrogradely degenerates (see ***Clinical case 13.5***); (2) the less conspicuous **mammillotegmental tract**, composed of collaterals of the mammillothalamic fibres. This tract projects to dorsal and ventral tegmental cell groups in the mesencephalon and the nucleus reticularis tegmenti pontis of Bechterew (Fry and Cowan 1972; Cruce 1977; Veazey et al. 1982; Ricardo 1983). These cell groups project back to the mammillary body via the **mammillary peduncle** (Nauta and Kuypers 1958; Cowan et al. 1964).

**Clinical Case 13.5 Unilateral Atrophy of the Mammillary Body Due to Damage of the Mammillothalamic Tract**

**Case report:** A 74-year-old male patient became comatose after acute gastrointestinal haemorrhage and died after 4 days. Six years before, he had a coronary bypass and had experienced left and right cardiac insufficiency several times. At autopsy, multiple infarctions were found, one of which was found in the right hypothalamus. This infarction included the mammillothalamic tract of Vicq d'Azyr (Fig. 13.14a, b). The right mammillary body was very atrophic and showed brown colouring, and histological examination showed extensive cell loss. The damage to the right mammillothalamic tract caused retrograde degeneration of neurons in the right mammillary body and, therefore, ipsilateral atrophy of this structure.

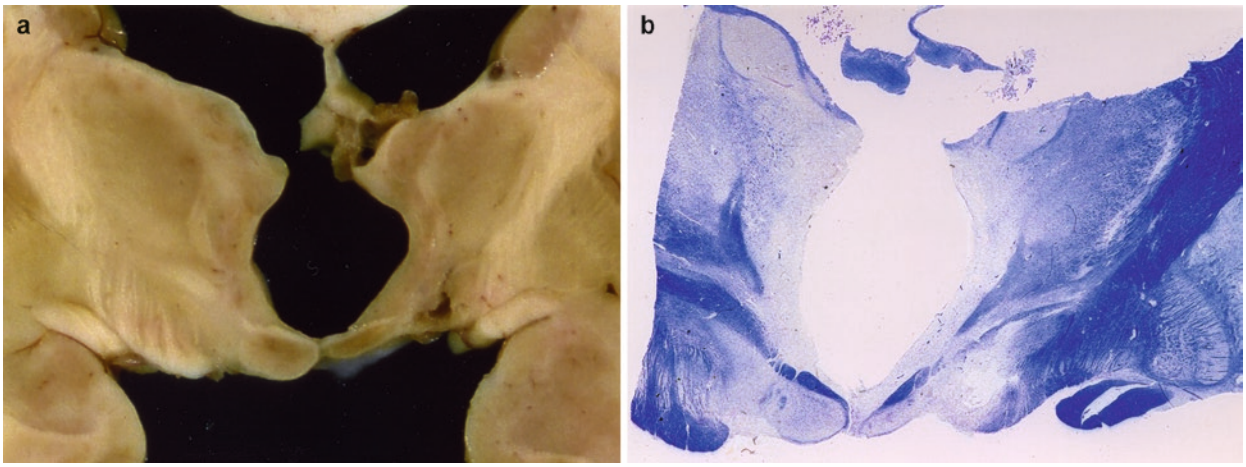



**Fig. 13.14** Unilateral atrophy of the mammillary body due to damage of the mammillothalamic tract: (**a**) frontal section of the brain; (**b**) LFB-stained section (courtesy Akira Hori, Toyohashi)

### 13.3.3 The Stria Terminalis

The **stria terminalis**, i.e. the **dorsal amygdalofugal pathway**, reciprocally connects the amygdaloid body and the medial hypothalamus (de Olmos and Ingram 1972; Lammers 1972; Fig. 13.15). In the region of the anterior commissure, the stria terminalis divides into different components, which innervate the bed nucleus of the stria terminalis, the medial hypothalamus and other areas in the basal parts of the forebrain. The stria terminalis is an important pathway for amygdaloid modulation of hypothalamic functions. The centromedial amygdala is also reciprocally related to the paraventricular, ventromedial and infundibular nuclei of the hypothalamus via the **ventral amygdalofugal pathway** (Price and Amaral 1981; Veening et al. 1984; see Chap. 14). The basolateral amygdala projects via the ventral amygdalofugal pathway to the lateral preoptico-hypothalamic zone (Nauta 1961; Krettek and Price 1978).

### 13.3.4 The Medial Forebrain Bundle

The MFB is probably the most complex fibre bundle in the brain (Nieuwenhuys et al. 1982; Veening et al. 1982; Vertes 1984a, b). At the junction of the diencephalon and the mesencephalon, the MFB fibres are rearranged into a smaller medial and a larger lateral stream (Holstege 1987). The *medial fibre stream* passes through the medial parts of the mesencephalic and rhombencephalic tegmental areas close to the raphe nuclei. It contains descending fibres from several hypothalamic centres to the raphe nuclei as well as ascending fibres from the raphe nuclei to the lateral hypothalamus and beyond (see Chap. 5). The *lateral fibre stream* sweeps laterally and caudally and descends through the mesencephalic central tegmental area to the lateral tegmental field of the pons and the medulla oblongata. It contains descending fibres from the central nucleus of the amygdala (Price and Amaral 1981; see Chap. 14), the bed nucleus of the stria terminalis

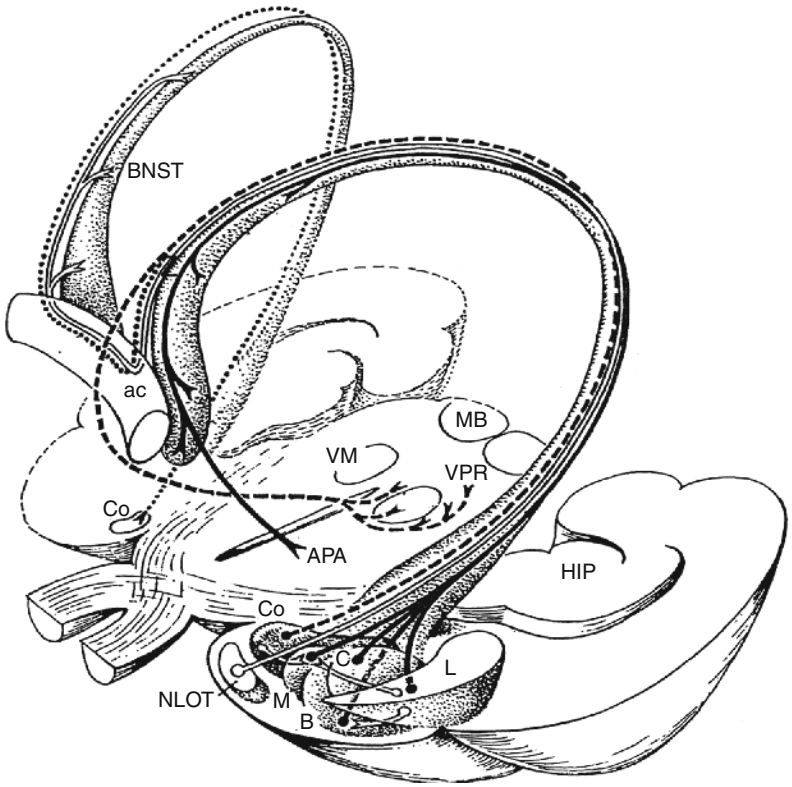



**Fig. 13.15** Connections of the stria terminalis as demonstrated in anterograde degeneration studies in cats. *ac* anterior commissure, *APA* anterior preoptic area, *B*, *C*, *Co*, *L*, *M* basal, central, cortical, lateral and medial amygdaloid nuclei, *BNST* bed nucleus of the stria terminalis, *HIP* hippocampus, *MB* mammillary body, *NLOT* nucleus of the lateral olfactory tract, *VM* ventromedial hypothalamic nucleus, *VPR* ventral premammillary region (after Lammers 1972)

(Holstege et al. 1985) and several hypothalamic areas (Holstege 1987; Luiten et al. 1987). These descending fibres terminate in a variety of brain stem centres including the pars compacta of the substantia nigra, the parabrachial nuclei, the locus coeruleus, the noradrenergic cell groups A1, A2 and A5, the superficial ventrolateral reticular area and the dorsal vagal complex. Most of these projections are reciprocal (Vertes 1984a, b). Descending hypothalamic fibres mainly arise in the paraventricular nucleus and the posterolateral hypothalamus (Saper et al. 1976a). So, the hypothalamus can directly influence preganglionic sympathetic and parasympathetic nuclei in the brain stem and the spinal cord (Saper et al. 1976a; Swanson and McKellar 1979; Swanson and Kuypers 1980; ter Horst 1986; Holstege 1987; Luiten et al. 1987). The existence of a similar pathway in the human brain can be inferred from the presence of an ipsilateral sympathetic deficit (***Horner syndrome***) following injury to the hypothalamus, the lateral brain stem tegmentum and the lateral funiculus of the spinal cord (Nathan and Smith 1986; Marx et al. 2004).

The hypothalamus provides extensive projections to the **cerebral cortex**. Physiological studies suggest that the hypothalamic projections to the cerebral cortex are essential for maintaining normal cortical arousal (Saper 1987; Risold et al. 1997). **Hypothalamocortical projections** arise mainly from the lateral tuberal nucleus and the posterior lateral hypothalamus. In an anterograde tracing study in rats, Saper (1985) showed that hypothalamocortical fibres pass via the MFB. In the preoptic area, one group of fibres turns laterally, ventral to the globus pallidus and the putamen, to enter the external capsule from which they are distributed to the neocortex of the lateral wall of the hemisphere. The remaining hypothalamocortical fibres follow the MFB rostrally and split up into two bundles: (1) one bundle joins the fornix to innervate the hippocampus and (2) another bundle runs over the genu of the corpus callosum into the cingulum bundle from which its axons are distributed to the cortex of the medial wall of the cerebral hemisphere.

In several species of monkeys, retrogradely labelled neurons have been found in the tuberal and posterior lateral

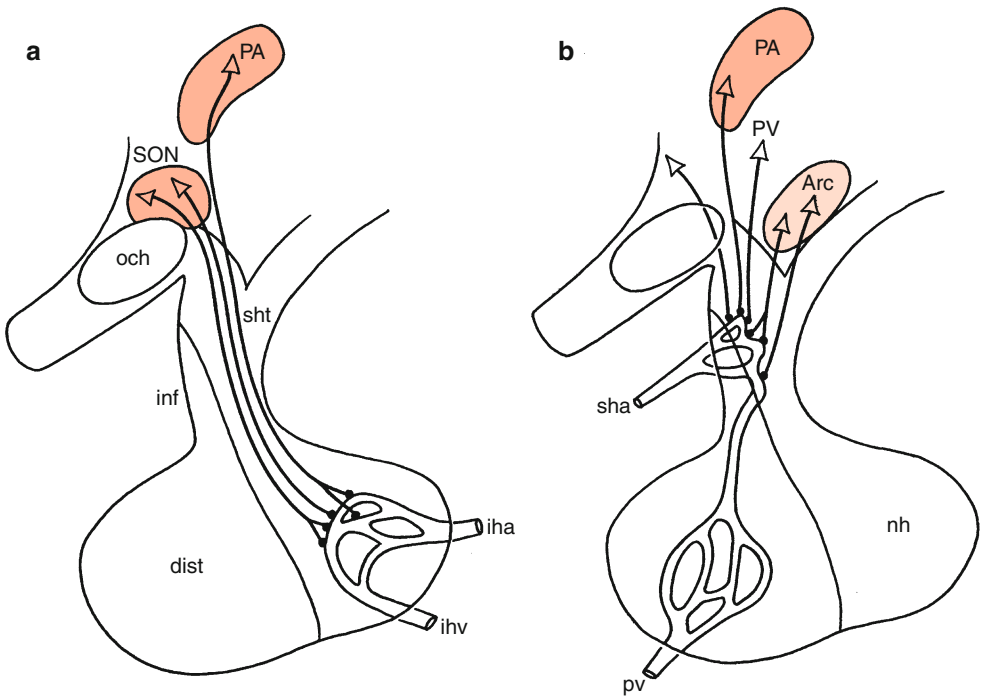



**Fig. 13.16** (**a**) The magnocellular and (**b**) the parvocellular secretory system. *Arc* arcuate nucleus, *och* optic chiasm, *dist* distal part of adenohypophysis, *inf* infundibular part of adenohypophysis, *iha*, *sha* inferior and superior hypohysial arteries, *ihv* inferior hypophysial vein, *nh* neurohypophysis, *PA* paraventricular nucleus, *pv* portal vein, *PV* periventricular region, *sht* supraopticohypophysial tract, *SON* supraoptic nucleus (after Heimer 1995)

hypothalamus following injections into the frontal, parietal and occipital cortices (Kievit and Kuypers 1975; Porrino and Goldman-Rakic 1982; Mesulam et al. 1983; Tigges et al. 1983; Rempel-Clower and Barbas 1998). The medial-to-lateral topography of the lateral hypothalamic projection to the cerebral cortex appears to be preserved in monkeys (Rempel-Clower and Barbas 1998). It has been suggested that the neurofibrillary degeneration of neurons in the brain stem and basal forebrain in Alzheimer disease may be due to retrograde transport of some pathogenetic agent from their terminals to the affected areas of the cerebral cortex (German et al. 1987; Saper et al. 1987). If this speculation is correct, then the distribution of NFTs in the hypothalamus may indicate that the hypothalamocortical projection in humans is organized in a manner similar to that in other mammalian species.

## 13.4 Hypothalamohypophysial Pathways

The hypothalamus is closely related to the hypophysis (see Fig. 13.3). The **magnocellular neuroendocrine system** is composed of axons from the large oxytocin- and vasopressin-containing neurons in the supraoptic and paraventricular nuclei that terminate in the posterior lobe of the pituitary. The **parvocellular neuroendocrine system** contains neurosecretory fibres from smaller neurons in the arcuate nucleus and other periventricular parts of the hypothalamus. These neurosecretory fibres project to the **median eminence**, where they terminate on the basal layers that line the perivascular spaces surrounding the capillary loops of the **hypophysial portal system**.

### 13.4.1 The Magnocellular Secretory System

The magnocellular supraoptic and paraventricular nuclei form the **supraoptico-** and **paraventriculohypophysial pathways** (Fig. 13.16a). These neurons produce vasopressin (the antidiuretic hormone, ADH) and oxytocin. The output from the supraoptic nucleus is primarily restricted to the neurohypophysis, whereas the paraventricular nucleus projects not only to the posterior lobe of the pituitary but also to the median eminence and to several extrahypothalamic regions including autonomic centres in the brain stem and the spinal cord. In immunohistochemical studies, the **vasopressinergic** and **oxytocinergic pathways** have been extensively studied (Swanson and McKellar 1979; Buijs et al. 1978; Sofroniew 1980). ***diabetes insipidus*** (***DI***) is characterized by polyuria and polydipsia. Thirst is the most prominent symptom of hypothalamic DI. Various types can be distinguished (see Swaab 2004): (1) familial central DI; (2) autoimmune Dl (3) pregnancy-induced DI; (4) as part of a midline developmental anomaly such as septo-optic dysplasia and holoprosencephaly (see Sarnat and Flores-Sarnat 2001) and (5) nephrogenic DI.

***Familial hypothalamic DI*** is transmitted as an autosomal dominant gene. Affected individuals have low or undetectable levels of circulatory vasopressin and suffer from polyuria and polydypsia but they respond to substitution therapy

with exogenous vasopressin or analogues. Members of a Dutch family suffering from this disease appeared to have a point mutation in one allele of the affected family members, based upon a G to T transversion at position 17 of the neurophysin encoding exon B on chromosome 20 (Bahnsen et al. 1992). Many other mutations were subsequently found (Rittig et al. 1996). The few postmortem histological observations in other families with hereditary hypothalamic DI suggest severe cell loss in the supraoptic and paraventricular nuclei (Breverman et al. 1965; Nagai et al. 1984; Bergeron et al. 1991).

***Wolfram syndrome*** (Wolfram 1938; or ***DIDMOAD***) is a disorder involving the presence of DI, diabetes mellitus, slowly progressive atrophy of the optic nerve and deafness (Cremers et al. 1977). It is an autosomal recessive hereditary syndrome. Juvenile diabetes mellitus and atrophy of the optic nerve, chiasm and tracts are the symptoms that occur most frequently in Wolfram syndrome (Scolding et al. 1996). The supraoptic and paraventricular nuclei are affected and the posterior lobe of the pituitary is largely absent (Carson et al. 1977). The vasopressin precursor is not processed in the hypothalamus of patients with Wolfram syndrome (Gabreëls 1998; Gabreëls et al. 1998). The gene involved (*WFS1* or *Wolframin*) encodes a putative transmembrane protein and was found on chromosome 4p16.1 (Inoue et al. 1998; Strom et al. 1998).

### 13.4.2 The Parvocellular Secretory System

The neurosecretory cells of the **parvocellular secretory system** are scattered throughout the periventricular zone and the preoptic area (Fig. 13.16b). There is a distinct localization for each of the hypothalamic-releasing hormones or factors that influence the anterior pituitary (see Swaab 1997, 2003). These hormones are transported axonally to the median eminence where they are released into the perivascular spaces surrounding the portal capillaries, formed by the superior hypophysial arteries (see Fig. 13.3). The portal capillaries join into the portal veins through which the hormones are transported to the vascular sinusoids in the adenohypophysis. Here, they influence the secretion of the pituitary hormones: TSH (thyroid-stimulating hormone or thyrotropin), ACTH, FSH, LH, GH (growth hormone or somatotropin) and PRL (prolactin).

Several releasing hormones have been localized immunohistochemically in the human brain. Thyrotropin-releasing hormone (TRH) cell bodies have been found in the paraventricular nucleus (Fliers et al. 1994). TRH is released in the median eminence as the major hypothalamic stimulating hormone of thyroid function, acting on TSH cells in the pituitary. Growth hormone-releasing hormone (GRH) has a rather limited distribution to the infundibular or arcuate nucleus in particular (Bloch et al. 1984; Pelletier et al. 1986). Neurons immunoreactive for LHRH are found mainly in the periventricular and arcuate nuclei (Barry 1977; Dudas et al. 2000). Additional LHRH-immunoreactive cells are found extending rostrally through the periventricular preoptic area as far as the lamina terminalis and up into the septum and caudally into the premammillary area and into the rostral midbrain. LHRH-immunoreactive fibres are found in the tubero-infundibular tract, ending on portal vessels in the median eminence and among the capillaries of the vascular organ of the lamina terminalis (Barry 1977). Corticotrophin-releasing hormone (CRH)-immunoreactive neurons are found primarily in the paraventricular nucleus (Pelletier et al. 1983). In humans and other primates, somatostatin (SOM)-immunoreactive neurons are not only found in the arcuate and periventricular nuclei with fibres extending into the neurohaemal contact zone in the median eminence but are also far more widely distributed (Bouras et al. 1987). SOM-immunoreactive neurons are found in the medial septal/diagonal band nuclei and nucleus basalis, the striatum and the bed nucleus of the stria terminalis as well as in the amygdala, the periaqueductal grey (PAG) and the brain stem reticular formation.

## 13.5 Functional Organization of the Hypothalamus

The hypothalamus receives a wide variety of different afferent inputs, which modulate specific drive states. It controls autonomic, endocrine and behavioural outputs. A key role in this circuitry is played by the SCN, the brain's biological clock. In Fig. 13.17, the major pathways are shown that translate the output from the SCN into circadian rhythms of sleep, feeding, corticosteroid secretion and body temperature (Saper et al. 2005a, b). The SCN sends the bulk of its output into a column that consists of the SPZ and the dorsomedial hypothalamic nucleus. Relays from the dorsal SPZ are necessary for organizing the circadian regulation of body temperature, which is controlled by the medial preoptic region. The ventral paraventricular zone, which is important for regulation of circadian rhythms of sleep and wakefulness as well as for locomotor activity, projects to the DMN. The DMN is critical for organizing circadian rhythms of sleep and wakefulness, feeding, locomotor activity and corticosteroid secretion. Feeding-related signals such as leptin or grelin influence circadian rhythm organization. These feeding cues enter the hypothalamus via the median eminence and are relayed by the ventromedial and arcuate nuclei to the SPZ and the DMN. Some aspects of hypothalamic control of feeding, reproduction, thermoregulation and sleep are discussed below. The role of the magnocellular secretory system has been discussed in Sect. 13.4.1. For the role of the hypothalamus in stress response, see de Kloet et al. (2005).

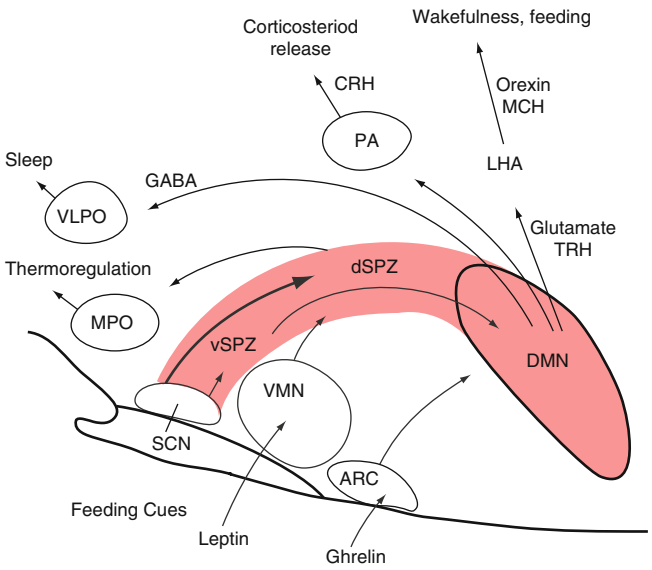



**Fig. 13.17** Summary diagram of the major pathways that translate the output from the suprachiasmatic nucleus into circadian rhythms of sleep, feeding, corticosteroid secretion and body temperature (see text for further explanation). *ARC* arcuate nucleus, *CRH* corticotropin-releasing hormone, *DMN* dorsomedial hypothalamic nucleus, *dSPZ* dorsal subparaventricular zone, *LHA* lateral hypothalamic area, *MCH* melanin-concentrating hormone, *MPO* medial preoptic nucleus, *PA* paraventricular nucleus, *SCN* suprachiasmatic nucleus, *TRH* thyrotropin-releasing hormone, *VLPO* ventrolateral preoptic nucleus, *VMN* ventromedial hypothalamic nucleus, *vSPZ* ventral subparaventricular zone (after Saper et al. 2005b)

### 13.5.1 Feeding

In 1901, Alfred Fröhlich observed the combination of obesity and lack of sexual maturation and suggested a role of the hypothalamus in feeding (Fröhlich 1901). These patients have pituitary tumours impinging on the medial basal hypothalamus. Fourty years later, Hetherington and Ranson (1942) placed stereotaxic lesions in the rat medial basal hypothalamus. They showed that lesions in a region, including the ventromedial, arcuate, dorsomedial and ventral premammillary nuclei, produced hyperphagia and obesity. This became known as the ***VMN syndrome***, although lesions restricted to the ventrolateral part of the VMN do not cause hyperphagia or obesity (Elmquist et al. 1999). An example is shown in ***Clinical case 13.1***. Lesions in the LHA dramatically reduce feeding (Hetherington and Ranson 1942).

These early observations have been explained by the discovery of a gene defect in the ***obese mouse*** as a functional deletion of the hormone leptin (Halaas et al. 1995; Elmquist et al. 1999). **Leptin** is released by white adipose tissue during times of metabolic substrate availability. Absence of leptin causes profound hyperphagia, reminiscent of the VMN syndrome. Leptin receptors have been found in highest concentrations in a group of nuclei, consisting of the arcuate nucleus, the dorsomedial part of the VMN, the posterior DMN and the ventral premammillary nucleus (Elmquist et al. 1998), in precisely the same region in which Hetherington and Ranson found the lesions that cause hyperphagia and obesity. Systemic leptin enters the CNS via the median eminence and binds in this same region (Banks et al. 1996; see Fig. 13.17). Elias et al. (1999, 2000) showed that leptin stimulates neurons in the arcuate nucleus that contain α-MSH/CART and inhibits neurons that contain neuropeptide Y (NPY) and agouti-related protein (AgRP). The α-MSH neurons are important for suppressing feeding as demonstrated by the hyperphagia and obesity found in rats that lack the melanocortin-4 receptor (Huszar et al. 1997). The α-MSH- and AgRP-containing neurons in the arcuate nucleus project to overlapping terminal fields in the paraventricular nucleus and the LHA (Elias et al. 1998), where they are believed to have mutually antagonistic effects. The paraventricular nucleus is thought to be important in promoting feeding. Also in rats, Gert ter Horst studied the projections of the paraventricular nucleus to the pancreas (ter Horst 1986; Luiten et al. 1987; Fig. 13.18b). The hypothalamus appears to control the hormone release from the pancreas not only by a direct autonomic modulation of the hormone-producing islet cells but also by way of an autonomic regulation of the blood stream in the pancreas.

The LHA contains two populations of neurons that express orexin/hypocretin and MCH (Elias et al. 1998). Both the orexin/hypocretin and the MCH neurons in the LHA are involved in feeding and metabolism. Both populations of neurons are innervated by the α-MSH/CART and the AgRP/NPY neurons in the arcuate nucleus (Elias et al. 1998; Broberger 1999). It seems likely that these rodent data can also be applied to humans. Elias et al. (1998) showed similar projections from the α-MSH/CART and AgRP/NPY neurons in the arcuate nucleus to both the orexin/hypocretin and the MCH neurons in the human lateral hypothalamus. These data provide strong evidence for the conservation of circuitry regulating feeding and body weight among mammals (Saper 2004).

### 13.5.2 Reproduction

Evidence from the leptin system also suggests that reproductive pathways are highly conserved between humans and other mammals (Saper 2004). Animals lacking leptin or its receptor are hyperphagic and hypogonadotropic, similar to the original description of Fröhlich syndrome (Elmquist et al. 1999). Physiological studies in rats and monkeys indicate that the **sexually dimorphic medial preoptic nucleus** is critical for male sexual performance (Arendash and Gorski 1983; Lloyd and Dixson 1988; for Fos-data, see Coolen 1995). Functional MRI data suggest that the same holds true for humans (Ferretti et al. 2005; Brunetti et al. 2008;

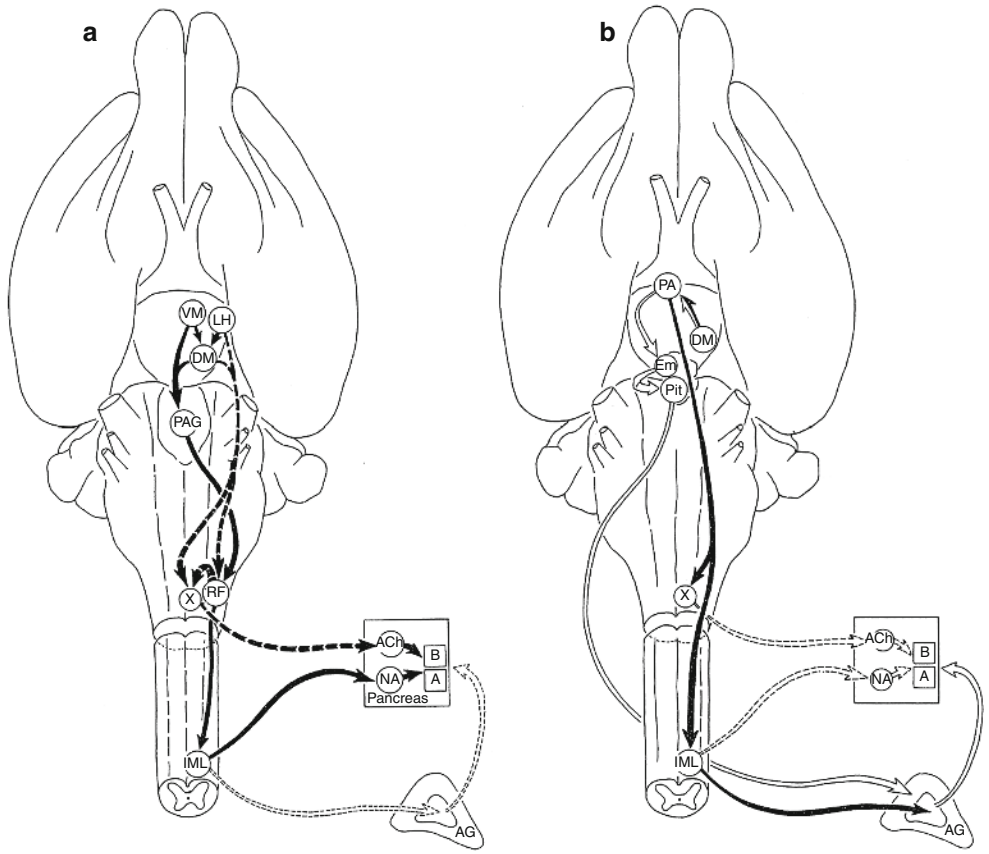



**Fig. 13.18** Diagrammatic representation of (**a**) the descending sympathetic and parasympathetic pathways originating from the lateral (*LH*), ventromedial (*VM*) and dorsomedial (*DM*) hypothalamic nuclei and (**b**) the outflow channels of the paraventricular nucleus (*PA*). In (**a**), direct projections from the lateral hypothalamic area and the dorsomedial nucleus are aimed at parasympathetic cells in the dorsal motor nucleus of the vagus nerve and the nucleus ambiguus (*X*). Indirect projections, relaying in the periaqueductal grey (*PAG*) and the lower medullary reticular formation (*RF*), are predominantly aimed at the sympathetic preganglionic cells in the intermediolateral column (*IML*). In (**b**), *black arrows* indicate neural autonomic connections to the various sympathetic and parasympathetic cell groups that innervate the gastrointestinal tract and related organs, here represented by the pancreas and the adrenal medulla (*AG*). The neuroendocrine connections to the adrenal cortex are indicated by open arrows and include releasing factors and hormonal circuits via the median eminence (*Em*) and the posterior pituitary gland (*Pit*). Other *abbreviations*: *A*, *B*-cell types in the pancreas, *ACh* acetylcholine, *NA* noradrenaline (after ter Horst 1986; courtesy Gert ter Horst, Groningen)

Fig. 13.19). For human PET data, see Holstege and Georgiadis (2003, 2004).

In rats, the medial preoptic nucleus is reciprocally connected with the ventrolateral part of the VMN, the ventral premammillary nucleus and the PAG (Simerly and Swanson 1988; Canteras et al. 1994). Recordings from the VMN in female monkeys demonstrate that neuronal firing increases during sexual stimulation (Auo et al. 1988). Lesions in the ventrolateral part of the VMN disrupt lordosis behaviour in female rats (Pfaff and Sakuma 1979). This response is thought to be mediated by projections from the VMN to the PAG in the midbrain (Simerly and Swanson 1988; Canteras et al. 1994; Kow and Pfaff 1998). In rodents, the caudolateral part of the PAG is involved in reproductive behaviour. In female rats, lordosis can be evoked by stimulation of this zone (Shipley et al. 1996). In cats, the caudal PAG receives spinal afferents from the contralateral lower lumbar and upper sacral spinal segments (VanderHorst et al. 1996). These projections arise in the area of termination of primary afferents from the vagina or penis, the pelvic floor and the peri-anal skin. In cats (VanderHorst and Holstege 1996) and monkeys (VanderHorst et al. 2000a, b), a compact group of neurons in the lateral PAG densely innervates the **nucleus retroambiguus**. This compact nucleus in the caudal medulla is not only involved in the control of respiration (see Chap. 12) but also projects to a distinct set of motoneurons in the lumbosacral cord that participates in producing female and male mating procedures (VanderHorst and Holstege 1995, 1996; VanderHorst et al. 2000a, b). In cats, this projection shows a remarkable dimorphism. Its density appears to depend on the estrogen cycle: it was almost nine times greater in estrous than in non-estrous females (VanderHorst and Holstege 1997).

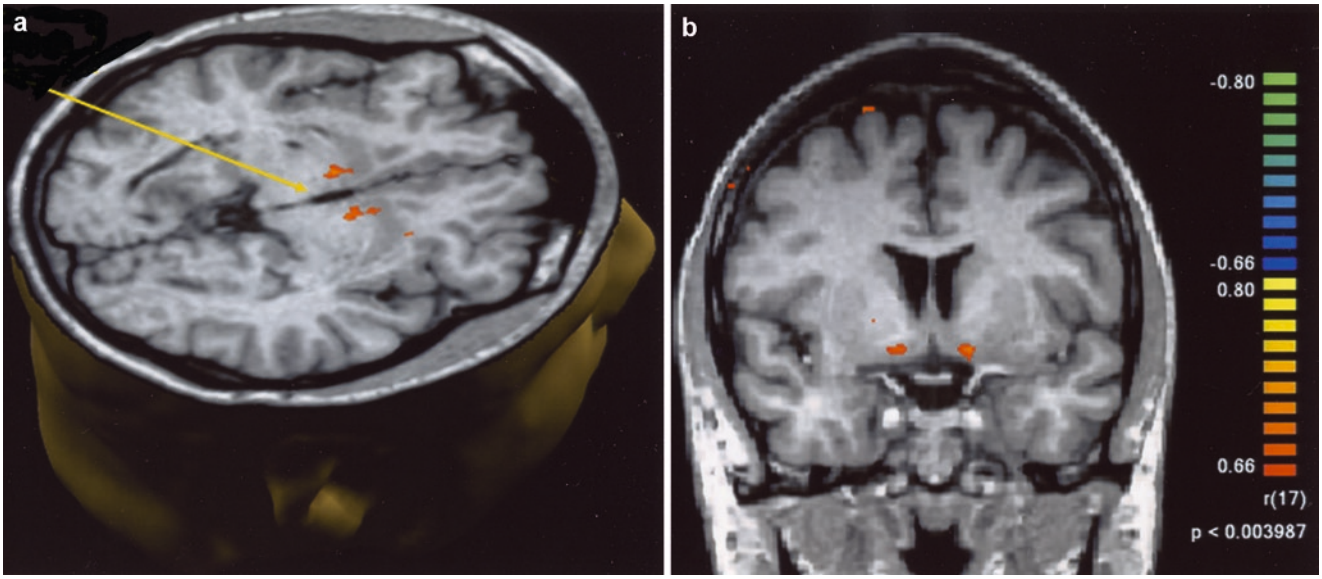



**Fig. 13.19** fMRI data on the dimorphic brain region in the medial preoptic area of a human male: (**a**) axial section, (**b**) coronal section, showing bilateral hypothalamic activation (after Brunetti et al. 2008; courtesy Marcella Brunetti, Chieti)

**Clinical Case 13.6 Pallister–Hall Syndrome**

***Pallister–Hall syndrome*** is a developmental disorder consisting of hypothalamic hamartoma, pituitary dysfunction, polydactyly and visceral malformations. This syndrome was first reported in infants (Clarren et al. 1980; Hall et al. 1980). It consists of hamartoblastomas of the hypothalamus with primitive, undifferentiated neurons. The disorder is inherited as an autosomal dominant trait with incomplete penetration, variable expressivity or gonadal or somatic mosaicism (Penman Splitt et al. 1994) and has been mapped to chromosome 7p13. Most cases are sporadic (Kuo et al. 1999). Hamartoblastomas probably arise in the fifth week of pregnancy and seem to be part of a complex pleitrophic congenital syndrome that includes absence of the pituitary, craniofacial abnormalities, cleft palate, malformations of the epiglottis or the larynx, congenital heart defects, hypopituitarism, short-limb dwarfism with postaxial polydactyly, anorectal atresia, renal anomalies and abnormal lung lobulation and hypogenitalism (see **Case report**).

**Case report:** Twins, born at the 35th week of gestation, both died shortly after birth. The first died on the second postnatal day with multiple malformations as the second child, but no autopsy was performed. The second child presented with multiple malformations such as facial dysmorphism, heptasyndactyly of the hands, hexadactyly of the feet and imperforate anus and died 6 days later due to anuria. At autopsy, other urogenital malformations were found including renal hypoplasia, ureter atresia and genital hypoplasia. Neuropathological examination revealed a large hamartoma of the hypothalamus and complete agenesis of the pituitary gland (Fig. 13.20). A diagnosis of ***Pallister–Hall syndrome*** was made. Histological examination showed 'matrix cell' aggregation with varying differentiation and a few ganglion-like cells.

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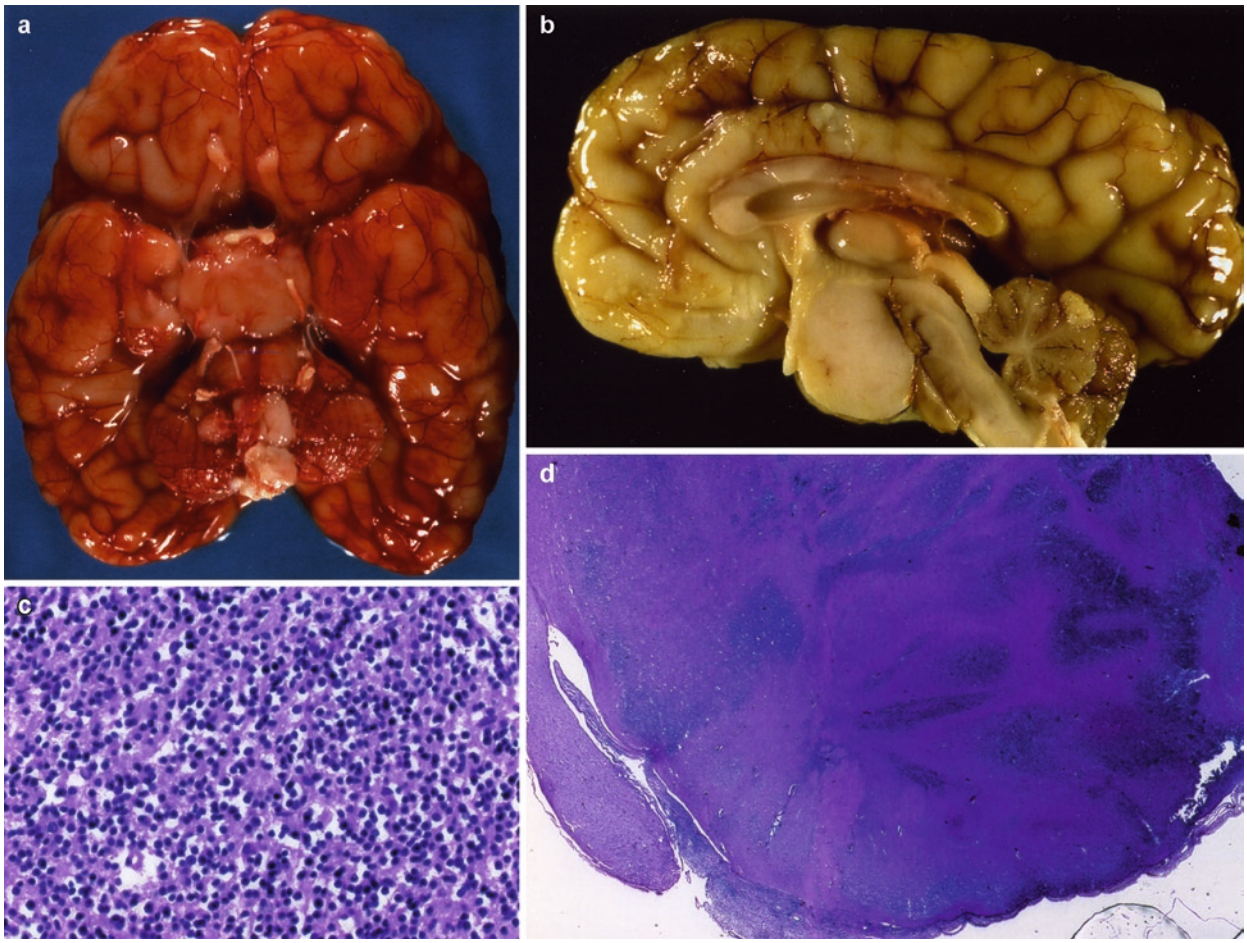


**Fig. 13.20** Basal view (**a**) and median section (**b**) of a foetal brain with ***Pallister–Hall syndrome***. The hamartoma of the hypothalamus (**d**) showed "matrix cell" aggregation (**c**; courtesy Akira Hori, Toyohashi)

### 13.5.3 Thermoregulation

The medial preoptic region in rats and monkeys is enriched in neurons that respond to local brain temperature (Hori et al. 1987; Griffin and Boulant 1995). The importance of the medial preoptic region in thermoregulation in humans is suggested by the rare disorder ***paroxysmal hypothermia*** (Plum and Van Uitert 1978). This disorder consists of intermittent attacks of decreased body temperature to as low as 27°C. It typically occurs in individuals who have had a developmental lesion of the anterior wall of the third ventricle including the medial preoptic region. In rats, the descending pathways from the preoptic area, that regulates thermogenesis, may involve projections through the ventrolateral part of the LHA to the PAG (Zhang et al. 1997; Chen et al. 1998). The PAG innervates the medullary raphe nuclei, which have a profound effect on thermoregulation (Morrison 1999).

### 13.5.4 Sleep

A role for the hypothalamus in the control for wakefulness and sleep has been known since Constantin von Economo's studies on patients with encephalitis lethargica (see Chap. 5). Von Economo (1920, 1930) predicted that the rostral hypothalamus contains sleep-promoting neurons, whereas the posterior hypothalamus contains neurons that promote wakefulness. His observations on the sleep-producing effects of injuries to the posterior lateral hypothalamus were reproduced by lesion studies in rats and monkeys (Ranson 1939; Nauta 1946). The **lateral hypothalamus** contains at least three populations of neurons that contribute to the regulation of **wakefulness** (Saper et al. 2001, 2005a, b). Neurons in the **perifornical group** producing **orexin** (Sakurai et al. 1998), also known as **hypocretin** (de Lecea et al. 1998), project to the cerebral cortex, the basal forebrain and the brain stem

arousal system (Peyron et al. 1998). These neurons co-express glutamate and maintain normal wakefulness (Estabrooke et al. 2001; Sakurai 2007). Lateral hypothalamic neurons that contain MCH have similar projections, but are most active during REM sleep (Saper et al. 2005a, b). Cell-specific lesions of the lateral hypothalamus cause severe sleepiness that is not seen in knockout mice of both orexin and MCH (Chemelli et al. 1999; Gerashchenko et al. 2003). Therefore, additional neurons in the lateral hypothalamus probably help to promote wakefulness.

In rats, Sherin et al. (1996, 1998) described a **sleep-promoting region** in the **ventrolateral preoptic area** (**VLPO**) of the rostral hypothalamus. The VLPO neurons produce GABA and the inhibitory peptide **galanin**. Saper et al. (2001) identified a corresponding cell group, containing galanin, in monkeys and humans. A **histaminergic** arousal system originates in the TMN and innervates the entire forebrain as well as brain stem regions that are involved in behavioural state control (Lin et al. 1996; Sherin et al. 1996; Saper et al. 2001). The rostral, galaninergic sleep-promoting and the caudal, orexinergic arousal-promoting regions of the hypothalamus are thought to be mutually inhibitory (Saper et al. 2001): the **sleep-switch** for hypothalamic control of sleep and wakefulness (see Chap. 5). During wakefulness, orexinergic neurons are active, stimulating monoaminergic nuclei, which causes arousal and inhibits the VLPO to prevent sleep. During sleep, the VLPO inhibits the monoaminergic groups and the orexinergic neurons, thus preventing arousal.

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