Chapter 1

Introduction: The middle and posterior hypothalamus

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SECTION 6[#]: SUPRAOPTIC AND PARAVENTRICULAR NUCLEUS: MORE THAN A NEUROENDOCRINE SYSTEM

Vasopressin and oxytocin are synthesized in the classic hypothalamic magnocellular *supraoptic and paraventricular* neuroendocrine *nuclei* (SON and PVN) and transported to the posterior pituitary. For basic information on this system in the human brain, on the development and the involvement of the fetal SON and PVN in the process of birth, on the effect of glucocorticoids on these neuroendocrine nuclei and on the periventricular nucleus (see Swaab, 2003, Chapter 8). An elaborate accessory magnocellular neuroendocrine system is present in the human hypothalamus, with contacts to the posterior pituitary and blood vessels. The neurohormone vasopressin acts as antidiuretic hormone on the kidney, while oxytocin is involved in uterine contractions in labor and in milk ejection. In addition, vasopressin and oxytocin, by their extra-hypothalamic projections, are critically involved in the modulation of socioemotional behavior, partner preference and sexual orientation, memory modulation, emotion regulation, and trust and pain perception and anticipation, often in a sexual dimorphic way. The PVN harbors, moreover, sympathetic and parasympathetic preautonomic neurons. Subpopulations of preautonomic neurons exist that are dedicated to, e.g., the control

of visceral and subcutaneous adipose tissue, liver and adrenal, skeletal muscle, and white and brown adipose tissue. Oxytocin is a multifunctional neuropeptide involved in the regulation of eating behavior, energy homeostasis, and metabolism, and oxytocin-based therapeutics are studied for treating obesity. Neuropeptide alterations in the SON and PVN during aging and in neurodegenerative disorders lead to different functional sequelae.

Three PVN systems have emerged as particularly relevant for anxiety disorders. First the oxytocin system is involved in social anxiety disorders. Second, the hypothalamic–pituitary–adrenal (HPA) axis is altered in in patients with panic disorder and generalized anxiety disorder by both, the central corticotropin-releasing hormone system and by cortisol. The third system is the hypothalamic–pituitary–thyroid axis that is likely to be compromised in panic disorder.

Animal models and humans exposed to stress in early life are more likely to suffer from long-term behavioral, mental, metabolic, immune, and cardiovascular health consequences. Early life experience is epigenetically programming stress–response genes in the central nodes of the HPA-axis, the hippocampus, and hypothalamus. Through DNA methylation, early life stress affects multiple physiological systems, including the metabolic and immune systems (Lucassen et al., 2013). DNA methylation programming early in life might cause gene

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expression changes later in life when and if the appropriate signals are present, e.g., under as stress. The interactions between the epigenetic matrix triggered by early stress and later events that modify the epigenome might result in reversal of early life adverse events or their aggravation.

Also the tripeptide thyrotropin-releasing hormone is produced by neurons in the PVN and has dense fiber networks in the hypothalamus (see Swaab, 2003, Chapter 8). As thyroid hormone is essential for the development of the brain in the first years of life, undiagnosed congenital hypothyroidism is one of the most common preventable causes of cognitive dysfunction. The identification of families with isolated central hypothyroidism, facilitated by T4-based neonatal screening, has helped to pinpoint several genes implicated in the pathogenesis of isolated central hypothyroidism.

SECTION 7: ZONA INCERTA

The *zona incerta* is integrated within a basal ganglia network and plays a role in sensory-motor programming. In addition, zona incerta's connections with the superior colliculus and the cerebral cortex as well as recent behavioral studies point to this region as playing a role in cognitive processes related to attention toward salient stimuli. The zona incerta, dorsal to the subthalamic nucleus, has become a target for deep brain stimulation in Parkinson's disease.

SECTION 8: VENTROMEDIAL NUCLEUS AND DORSOMEDIAL NUCLEUS

The *dorsomedial and ventromedial hypothalamic nuclei* are critical for numerous behaviors, including those in response to psychological stressors. These behaviors are coupled with changes in autonomic function, such as altered blood pressure, thermogenesis, heart rate, sympathetic nerve activity, resetting of the baroreflex, and changes in pituitary function. In addition, they could also be responsible for hypertension associated with obesity. Recent human brain imaging studies have provided the first evidence that the DMH and VMH are involved in regulating resting muscle sympathetic nerve activity levels in awake, healthy humans in the absence of any ongoing stress. The cytoarchitecture and in and output of these nuclei are described in Swaab (2003, Chapters 9 and 10).

SECTION 9: CIRCUMVENTRICULAR ORGANS OF THE HYPOTHALAMUS

The *subfornical organ*, the *organum vasculosum of the terminalis*, and the *median preoptic nucleus* comprise the *lamina terminalis*. These structures play a role in integrating the control of multiple autonomic systems and so in cardiovascular regulation and the control of fluid balance. Circulating angiotensin II acts at the subfornical

organ to stimulate drinking and increase blood pressure. Antibodies against the NaX-channel expressing neurons of the subfornical organ cause hypernatremia in patients. There is also evidence suggesting roles for regions of the lamina terminalis in reproduction, respiration, food intake, and immune function. The lamina terminalis is nowadays used as a surgical corridor for the microsurgical treatment of several conditions such as obstructive hydrocephalus and diencephalic tumors.

The *infundibular nucleus (in rodents "arcuate nucleus")* forms a morphologic and functional entity with the median eminence and contains neurons that are controlling prolactin release, food intake, and metabolism as well as reproduction and onset of puberty. The median eminence lacks a blood–brain barrier and provides an entry to monitor for peripheral signals, such as nutrients, leptin, and ghrelin. Neurons of the infundibular nucleus contribute to the tubero-infundibular tract terminating in the median eminence on the hypophysial portal vessels and regulate the anterior lobe of the pituitary. Infundibular nucleus neurons are reciprocally connected with several other hypothalamic nuclei, the brainstem, and reward pathways. The hypophysial pars tuberalis is attached to the stalk of the pituitary and median eminence and controls seasonal functions. In the median eminence, tanycytes take over the blood–brain barrier function. These ependymo-glial cells form the wall of the third ventricle and send long extensions into the parenchyma to contact blood vessels and hypothalamic neurons. Tanycytes control the transport of hormones and key metabolites in and out of the hypothalamus and play a key role in regulating glucose balance, food intake, endocrine axes, seasonal changes, reproductive function, and aging.

Kisspeptin neurons regulate the onset of puberty, account for the pulsatile secretion of gonadotropin-releasing hormone (GnRH) and mediate negative and positive estrogen feedback signals to GnRH neurons. There are major kisspeptin cell groups in the preoptic area/rostral hypothalamus and infundibular nucleus that integrate various types of environmental, endocrine, and metabolic signals that can influence fertility. Kisspeptin neurons that cosynthesize the tachykinin peptide neurokinin B (NKB) and the opioid peptide dynorphin are called KNDy neurons. The absence of negative estrogen feedback in menopause cause considerably higher kisspeptin and NKB activities. The increased NKB signaling toward the preoptic thermoregulatory centers plays a crucial role in hot flushes. NK3R is the receptor for NKB. NK3R antagonists are emerging as a new treatment for menopausal hot flushes. In addition, kisspeptin-54 has been used in clinical practice as a safe trigger of oocyte maturation in women undergoing in vitro fertilization treatment who are also at high risk of developing ovarian hyperstimulation syndrome.

Women have higher kisspeptin and NKB expression in the infundibular nucleus than men. Kisspeptin and NKB are often coexpressed but not with dynorphin in postmortem material, thereby challenging the KDNy concept in humans. Female-typical expression of both kisspeptin and NKB were observed in the infundibular nucleus of male to female transsexual people, suggesting an atypical sexual differentiation of the brain.

In addition, the infundibular nucleus is the main regulator of energy homeostasis. The peptidergic neurons, astrocytes and microglia in the infundibular nucleus receive from the circulation metabolic cues like insulin, leptin, glucose, and fatty acids, to monitor the energy state of the body. All these metabolic cues are integrated into an output signal regulating energy homeostasis through the release of neuropeptides. Proopiomelanocortin expressing neurons inhibit food intake and stimulate energy expenditure, whereas the agouti-related protein/neuropeptide Y expressing neurons stimulate food intake and inhibit energy expenditure. Dysfunctional regulation of energy homeostasis results in increased bodyweight and obesity, eventually leading to type 2 diabetes mellitus. Neurodegenerative disorders such as amyotrophic lateral sclerosis and frontotemporal dementia develop prominent changes in weight and eating behavior. These changes include alterations in metabolism, lipid levels, and insulin resistance. Emerging research suggests that these alterations may be mediated through changes in the hypothalamic function, but the exact mechanisms have still to be revealed.

SECTION 10: LATERAL TUBERAL NUCLEUS

The *lateral tuberal nucleus* (LTN) is a hypothalamic region that has been identified with certainty only in humans and primates. For information on the human LTN in health and disease (see Swaab, 2003, Chapter 12). A parvalbumin-positive (PV1) nucleus in the lateral hypothalamus of rodents was proposed to be possibly homologous to the human LTN. The human LTN is intensely immunoreactive for somatostatin and FF1, but only weakly so or not at all for parvalbumin, calbindin, and calretinin. The rodent PV1-nucleus is intensely immunoreactive for parvalbumin but is not immunoreactive for either somatostatin, FF1, calbindin, or calretinin. Consequently, it was so far not possible to demonstrate a neurochemical homology between the human LTN and the rodent PV1-nucleus (Gerig and Celio, 2007; Mészár et al., 2012).

SECTION 11: LATERAL HYPOTHALAMIC AREA, PERIFORNICAL AREA

Hypocretin-1 and -2 (or "orexin A and B") are neuropeptides exclusively produced by a group of neurons in the lateral and dorsomedial hypothalamus that project throughout the brain and act by their respective receptors. The hypocretin system is involved in sleep–wake regulation, reward mechanisms, food intake and metabolism, autonomic regulation including thermoregulation, and pain. The sleep disorder narcolepsy type 1, which is likely due to an autoimmune process, is caused by a 90% loss of hypocretin neurons. In addition, may the hypocretin system also be affected, but to a lesser extent and less specifically, in neurodegenerative diseases such as Alzheimer's, Huntington's, and Parkinson's disease, immune-mediated disorders such as multiple sclerosis, neuromyelitis optica and anti-Ma2 encephalitis, and genetic disorders such as type 1 diabetus mellitus and Prader–Willi syndrome.

Human heroin addicts have an increased number of hypocretin neurons, which are substantially smaller than those staining for hypocretin in control brains. It is proposed that an increased number of hypocetin neurons may underlie and maintain opioid or cocaine use disorders. Human narcoleptics, despite their prescribed use of several commonly addictive drugs, do not show significant evidence of dose escalation or substance use disorder.

SECTION 12: TUBEROMAMILLARY COMPLEX

The *tuberomamillary neurons* in the posterior hypothalamus produces histamine and this nucleus innervates a large number of brain areas. The histaminergic system controls several basal physiological functions, including the sleep–wake cycle, energy and endocrine homeostasis, sensory and motor functions, and cognitive functions such as attention, learning and memory. Four G protein-coupled receptors mediate these effects. The two classic histamine postsynaptic receptors, the H1 and H2 receptors, mediate many of the central effects of histamine on, e.g., alertness and wakefulness. The H3 receptor is a pre- and postsynaptic receptor, which regulates release of histamine and several other neurotransmitters, including serotonin, GABA, and glutamate. H4 receptor is found in cerebral blood vessels and microglia. The H3 receptor antagonist Pitolisant is used to treat narcolepsy and hypersomnia. H1 receptor antagonists have been used to treat insomnia and H2 receptor antagonists have shown efficacy in treatment of schizophrenia. Histaminergic dysfunction may contribute to clinical disorders such as Parkinson's disease, Alzheimer's disease, Huntington's disease, narcolepsy type 1, schizophrenia, Tourette syndrome, and autism spectrum disorder. H_4R might indeed be a therapeutic target for Parkinson's disease acting via microglia inhibition.

SECTION 13: SUBTHALAMIC NUCLEUS

The *subthalamic nucleus* increases the inhibitory drive of the basal ganglia. It has gained substantial interest as a target for deep brain stimulation for a variety of movement disorders. The level of overlap between putative limbic, associative, and motor zones within this nucleus is still debated. MRI and postmortem microscopic anatomical are now combined into an integrative research approach of this problem. Deep brain stimulation of the subthalamic nucleus is generally successful but can be complicated by adverse neuropsychiatric side effects, most commonly characterized by impulsivity and mood elevation, although depression, anxiety, apathy, and cognitive changes have also been reported. Deep brain stimulation of the subthalamic nucleus is now also employed to treat obsessive–compulsive disorder.

The high rate of *placebo responses in Parkinson's disease* clinical trials provided the impetus for investigating the underlying mechanisms. Specifically, placebo effects are associated with dopamine release in the striatum and changes in neuronal activity in the subthalamic nucleus, substantia nigra pars reticulata, and motor thalamus in Parkinson's disease, as assessed through positron emission tomography and single-neuron recording during deep brain stimulation. Conversely, verbal suggestions of clinical worsening or drug dose reduction induce nocebo responses in Parkinson's disease, which have been detected at both behavioral and electrophysiologic level. An important implication of this knowledge is that in clinical trials patients' expectations should always be assessed.

SECTION 14: CORPORA MAMILLARIA, FORNIX, AND MAMILLOTHALAMIC TRACT

The *corpora mamillaria*, their input by the fornix, and the mamillothalamic tract are involved in cognition. For the changes in these structures in Alzheimer's disease and other neurodegenerative disorders, schizophrenia, and the effects of lesions (see Swaab, 2003, Chapter 16). The fornix has gained recent interest as potential deep brain stimulation target to decrease rates of cognitive decline, enhance memory, aid visuospatial memorization and improve verbal recollection. Studies reported enhanced hippocampal acetylcholine release, synaptic plasticity, and decreased inflammatory responses in cortex and hippocampus. However, it is still premature to conclude that fornix deep brain stimulation can be used in the treatment of cognitive disorders.

Histopathological alterations of the mamillary bodies occur after severe thiamine deficiency in combination with alcohol abuse in *Wernicke's encephalopathy* and in the residuals of this disorder *Korsakoff's syndrome* and *Korsakoff's psychosis*. As a rule, Wernicke's encephalopathy always occurs alongside neuropathology in other subcortical gray matter structures, notably the medial thalamus. When Wernicke's encephalopathy is treated early in the process by large quantities of thiamine, full clinical recovery is likely to occur. As a residual syndrome after Wernicke's encephalopathy, Korsakoff's syndrome should be considered a form of acquired brain damage and pharmacological therapy is not effective. However, there is accumulating evidence that memory rehabilitation may possible in Korsakoff's syndrome to a certain degree.

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