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Review

Signaling pathways to and from the hypophysial pars tuberalis, an important center for the control of seasonal rhythms

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ABSTRACT

Seasonal (circannual) rhythms play an important role for the control of body functions (reproduction, metabolism, immune responses) in nearly all living organisms. Also humans are affected by the seasons with regard to immune responses and mental functions, the seasonal affective disorder being one of the most prominent examples. The hypophysial pars tuberalis (PT), an important interface between the hypophysial pars distalis and neuroendocrine centers in the brain, plays an essential role in the regulation of seasonal functions and may even be the seat of the circannual clock. Photoperiodic signals provide a major input to the PT. While the perception of these signals involves extraocular photoreceptors in non-mammalian species (birds, fish), mammals perceive photoperiodic signals exclusively in the retina. A multisynaptic pathway connects the retina with the pineal organ where photoperiodic signals are translated into the neurohormone melatonin that is rhythmically produced night by night and encodes the length of the night. Melatonin controls the functional activity of the mammalian PT by acting upon MT1 melatonin receptors. The PT sends its output signals via retrograde and anterograde pathways. The retrograde pathway targetting the hypothalamus employs TSH as messenger and controls a local hypothalamic T3 system. As discovered in Japanese quail, TSH triggers molecular cascades mediating thyroid hormone conversion in the ependymal cell layer of the infundibular recess of the third ventricle. The local accumulation of T_3 in the mediobasal hypothalamus (MBH) appears to activate the gonadal axis by affecting the neuro-glial interaction between GnRH terminals and tanycytes in the median eminence. This retrograde pathway is conserved in photoperiodic mammals (sheep and hamsters), and even in non-photoperiodic laboratory mice provided that they are capable to synthesize melatonin. The anterograde pathway is implicated in the control of prolactin secretion, targets cells in the PD and supposedly employs small molecules as signal substances collectively denominated as "tuberalins". Several "tuberalin" candidates have been proposed, such as tachykinins, the secretory protein TAFA and endocannabinoids (EC). The PT-intrinsic EC system was first demonstrated in Syrian hamsters and shown to respond to photoperiodic changes. Subsequently, the EC system was also demonstrated in the PT of mice, rats and humans. To date, 2-arachidonoylglycerol (2-AG) appears as the most important endocannabinoid from the PT. Likely targets for the EC are folliculo-stellate cells that contain the CB1 receptor and appear to contact lactotroph cells. The CB1 receptor was also found on corticotroph cells which appear as a further target of the EC. Recently, the CB1 receptor was also localized to CRF-containing nerve fibers running in the outer zone of the median eminence. This finding suggests that the EC system of the PT contributes not only to the anterograde, but also to the retrograde pathway. Taken together, the results support the concept that the PT transmits its signals via a "cocktail" of messenger molecules which operate also in other brain areas and systems rather than through PT-specific "tuberalins". Furthermore, they may attribute a novel function to the PT, namely the modulation of the stress response and immune functions.

1. Seasonal rhythms

Organisms living in higher latitudes of the world experience profound seasonal changes in the environment, e.g. temperature and daylength. Such seasonal rhythms play an important role for the control of several body functions, e.g., reproduction, metabo-

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lism and immune responses. Adaptation to these changes involves intrinsic mechanisms, the so-called circannual clock (Lincoln et al., 2006; Wood et al., 2015) and environmental stimuli. The most important environmental stimulus is the seasonally varying length of day and night, i.e., the photoperiod. The photoperiod (day length) is measured by the circadian system which oscillates with a period of approximately 24 h (cf. Ikegami and Yoshimura, 2016). Seasonal rhythms are of high relevance for biodiversity and modern societies facing climate change (Stevenson et al., 2015). They also affect human welfare, seasonal affective disorder being one of the most prominent examples (see Wirz-Justice, this volume). Recent studies have revealed a conspicuous seasonal variation in human immunity (Dopico et al., 2015): during European winter the human immune system shows a profound pro-inflammatory profile and levels of soluble IL-6 receptor and C-reactive protein are increased. The latter are considered as risk biomarkers for cardiovascular, psychiatric and autoimmune diseases that have peak incidences in winter. In accord with these experimental data modelling studies predict that the proinflammatory state predominates during the winter months (Pierre et al., 2016).

Given the physiological and pathophysiological relevance of seasonal rhythms the structures and circuits involved their regulation are of particular interest. As shown by comprehensive studies with photoperiodic animals over the last decades, the hypophysial pars tuberalis (PT) represents a mandatory structure for the control of seasonal behavior and metabolism (cf. Yasuo and Korf, 2011). This review will thus focus on the structure as well as the input and output pathways of the PT.

2. Location and cell types of the pars tuberalis

The pars tuberalis (PT) is the rostral part of the adenohypophysis and develops from the lateral lobes of Rathke's pouch which grow toward the rostroventral region of the infundibulum. The PT is in close vicinity to the external layer of the median eminence, the portal vasculature, and the hypophysial pars distalis (PD) and is also connected with the third ventricle partially via processes of tanycytes in the infundibular recess and median eminence (Fitzgerald, 1979; Guerra et al., 2010). In rodents (rat, hamster, mouse) the pars tuberalis (PT) consists of a median part which comprises a few cell layers and stretches out from the rostralmost to the caudalmost parts of the PT. In its caudal part the PT forms more compact lateral extensions (Fig. 1).

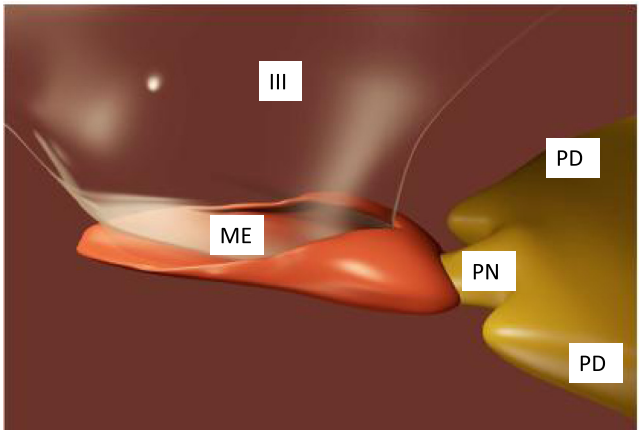

Fig. 1. Three dimensional reconstruction of the murine mediobasal hypothalamus including the pars tuberalis (red), third ventricle (III), median emincence (ME), Pars nervosa (PN) and pars distalis (PD). View from lateral. Courtesy of Nina-Kim Kröher and Helmut Wicht, Frankfurt am Main.

The PT comprises several cell types including (1) PT-specific cells, the most abundant cell type in the PT, (2) follicular cells, small cells devoid of secretory features, and (3) displaced PD-cells characterized by a high number of secretory granules (Stoeckel and Porte, 1984; Gross, 1984; Pelletier et al., 1992, 1995). The PT-specific cells exhibit all characteristics of peptide-secreting cells but can be distinguished from any cell type in the PD (Wittkowski et al., 1999). PT-specific cells contain high levels of melatonin receptor MT1 (rat: Klosen et al., 2002; European hamster: Dardente et al., 2003) at variance with the cells in the PD which express melatonin receptors only transiently during late fetal development (Vanecek, 1988). Most PT-specific cells show immunoreactivities for the beta-subunit of thyrotropin (TSHB) and the common glycoprotein alpha-subunit (CGA) in various mammalian species including rats, Siberian hamsters, mice and man (Bockers et al., 1994; Stoeckel et al., 1994; Yasuo et al., 2009). Despite the fact that transcripts of *TSHB* are of identical size and sequence in the PT and the PD (Bockmann et al., 1997), the regulation of gene expression differs between the PT-specific cells and the thyrotrophs in the PD: the thyrotrophs in the PD are endowed with triiodothyronine (T_3)- or TSH-releasing hormone (TRH)-receptors, which are essential for the classical feedback mechanisms in hypothalamic-pituitary-thyroid axis (Bockmann et al., 1997). The PT-specific cells, however, lack these receptors and are regulated by the photoperiod and melatonin signals (Bockmann et al., 1996; Wittkowski et al., 1988). Already these early data have suggested specialized functions of TSH in PT-specific cells which might be associated with the transduction of photoperiodic stimuli.

3. The molecular clockwork of the pars tuberalis and its photoperiodic regulation

Shortly after the cloning of the first clock genes, their expression was demonstrated in the pars tuberalis as one of the first peripheral oscillators (Sun et al., 1997; Zylka et al., 1998). Since then, numerous comprehensive studies have confirmed that the mammalian PT comprises a molecular clockwork consisting of transcriptional activators, Circadian Locomotor Output Cycles Kaput (CLOCK) and aryl hydrocarbon receptor nuclear translocator-like 1 (BMAL1), and of transcriptional inhibitors, PER1-2 and CRY1-2, the most important components of the molecular clockwork (Reppert and Weaver, 2002). *Cry1*-mRNA levels peak at midnight, while *Per1*-mRNA levels reach a maximum during early day (Dardente et al., 2003; Johnston et al., 2005; Lincoln et al., 2002; Messager et al., 1999; von Gall et al., 2002a, 2005). Regardless of this time difference, the protein levels of both, mPER1 and mCRY1 were shown to be high in the murine PT during midday (Jilg et al., 2005). A molecular clockwork has also been demonstrated in the avian PT (Yasuo et al., 2003, 2004).

At the organ level, the rhythm in the PT is not self-sustained, but its maintenance requires photoperiodic input. In avian species photoperiodic signals are perceived by deep brain (encephalic) photoreceptors (Foster et al., 1985; Ikegami and Yoshimura, 2016; Kuenzel, 1993; Nakane et al., 2010) and do not require the melatonin signal from the pineal organ (Gwinner et al., 1997). Several attempts were made to localize these encephalic photoreceptors and their photopigments. Hypothalamic neurons which project to the internal layer of the median eminence in Japanese quail and chicken were shown to express *vertebrate ancient* (*VA*)-opsin (Halford et al., 2009). A novel mammalian neural tissue opsin (Opsin 5) has been demonstrated in cerebrospinal fluid-contacting neurons of the paraventricular organ (PVO) and their axonal projections to the external layer of the median eminence, which is in close vicinity to the PT (Nakane et al., 2010). The PVO exists in

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