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Review

Seasonal regulation of structural plasticity and neurogenesis in the adult mammalian brain: Focus on the sheep hypothalamus

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ABSTRACT

To cope with variations in the environment, most mammalian species exhibit seasonal cycles in physiology and behaviour. Seasonal plasticity during the lifetime contributes to seasonal physiology. Over the years, our ideas regarding adult brain plasticity and, more specifically, hypothalamic plasticity have greatly evolved. Along with the two main neurogenic regions, namely the hippocampal subgranular and lateral ventricle subventricular zones, the hypothalamus, which is the central homeostatic regulator of numerous physiological functions that comprise sexual behaviours, feeding and metabolism, also hosts neurogenic niches. Both endogenous and exogenous factors, including the photoperiod, modulate the hypothalamic neurogenic capacities. The present review describes the effects of season on adult morphological plasticity and neurogenesis in seasonal species, for which the photoperiod is a master environmental cue for the successful programming of seasonal functions. In addition, the potential functional significance of adult neurogenesis in the mediation of the seasonal control of reproduction and feeding is discussed.

1. Introduction

Animals that live in a temperate latitude must cope with seasonal fluctuations in climate, temperature and food availability. To anticipate these environmental changes and program biological functions and behaviours accordingly, adaptive strategies have been developed that consist of the seasonal timing of reproductive and metabolic functions. Animals rely on the photoperiod, which is the most reliable environmental cue to adapt their physiology to the changing environment.

The hypothalamus, a key homeostatic structure, is critically involved in the control of numerous physiological functions including reproduction, energy intake/expenditure balance and thermoregulation, as well as their seasonal regulation. The hypothalamus-dependent homeostatic and neuroendocrine regulations are ensured by several anatomically distinct nuclei that integrate afferent signals from the periphery and treat efferent signals. For example, gonadotropin-releasing hormone (GnRH), the key hormonal regulator of reproductive function, is produced by a scattered network of neurons located in the hypothalamic preoptic area that project to the median eminence (ME); it is released into the anterior pituitary via the hypothalamo-hypophyseal portal circulation, from where it stimulates the gonadal axis. From the seminal lesion studies performed in rodents during the previous century (Brobeck, 1946; Hetherington and Ranson, 1940) to the use of recently developed optogenetic techniques that have provided detailed temporal and spatial control information regarding the activity of the hypothalamic neural circuits (Aponte et al., 2011; Atasoy et al., 2012), the hypothalamus is recognised as the central structure that regulates feeding, satiety and energy balance (review in Schneeberger et al. (2014)).

Understanding the mechanisms that underlie the annual programming of these physiological functions by environmental cues is essential to decipher the functional adaptation of brain to the changing environmental conditions. One ever growing field of interest comprises the investigation of the potential involvement of plasticity mechanisms, including structural/morphological and cellular plasticity (cytogenesis/neurogenesis), in such regulations. Morphological plasticity of the adult hypothalamus, which includes changes in the sizes and shapes of neurons and alterations in their inputs and outputs, is a phenomenon known to generate

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appropriate outcomes regarding the responsiveness to both endogenous and environmental signals during prenatal and post natal life (Plant and Shahab, 2002; Tasker et al., 2002; Theodosis et al., 2004; Naftolin et al., 2007; Prevot et al., 2010). Seasonal adaptions in physiology and behaviour also involve variations in brain volume and neurogenesis, and these changes that have been particularly well described in various species of birds. The groundbreaking experiments using [^{3}H]thymidine to identify dividing cells has led to the discovery that new neurons were generated and integrated into functional avian song circuits under a photoperiodic control (Goldman and Nottebohm, 1983; Paton and Nottebohm, 1984). This evidence was the first unambiguous demonstration that the photoperiod can regulate neurogenesis in adult vertebrate brains. The adult mammalian brain has long been thought to have a static organisation and the production of new neurons or neurogenesis was believed to be restricted to the embryonic stages of central nervous system (CNS) development. However, growing bodies of evidence indicate that the adult brains of all mammals, including humans, can generate new neurons and glial cells in a constitutive way throughout life (Eriksson et al., 1998; Doetsch et al., 1999; Alvarez-Buylla and Lim, 2004).

Reproduction and food intake/metabolism are two intermingled physiological functions tightly controlled by photoperiod in seasonal mammals. Following a brief review of the seasonal regulations of the neuroendocrine networks involved in these functions, (Section 2), we discuss recent findings regarding the seasonal regulations of structural plasticity (Section 3) and neurogenesis mechanisms in mature brains of seasonal species (Section 4). Finally, future research directions are proposed that could link new neuron production to the seasonal adaptation of neuroendocrine networks (Section 5).

2. Timing of reproductive and metabolic physiology in seasonal mammals

2.1. Reproduction in seasonal mammals

Large mammalian species, including sheep, goats and red deer, that have long gestation periods of nearly 6 months breed when day lengths are decreasing, i.e., during the fall through mid-winter, and are thus referred to as short-day breeders. In contrast, mammals with short gestation periods of a several weeks, including hamsters, shrews, voles and deer mice, breed in late winter/early spring at a time when day lengths are increasing and are therefore referred to as long-day breeders. Nevertheless, for both types of seasonal breeders, the birth of the progeny occurs in spring/midsummer when food is abundant and temperatures clement, which provides propitious conditions for the appropriate development of the young prior to the harsh environmental conditions of the subsequent winter. In vertebrates this seasonal regulation of reproductive activity is sustained by the annual arousal of the hypothalamic–pituitary–gonadal (HPG) axis.

In sheep, the breeding season is initiated at the beginning of autumn and is completed in late winter or at the very beginning of spring, and it is characterised by a succession of 16- to 18-day estrous cycles (Karsch et al., 1984). Similar to many seasonal breeders, the ovine HPG axis is controlled by the photoperiod through changes in the secretion of the pineal hormone melatonin (Karsch et al., 1986; review in Goodman and Inskeep (2006)). The photoperiodic information is perceived by melanopsin-containing retinal ganglion cells and is transmitted as a neural signal via the suprachiasmatic nucleus, the paraventricular nucleus (PVN) and the superior cervical ganglion to the pineal gland. From there, neural sympathetic afferences control nocturnal melatonin production (review in Malpaux (2006)). Overall, the nocturnal duration of melatonin production reflects the annual variations of the photoperiod. Thus, the daily melatonin secretion pattern is considered an endocrine index of the external photoperiod.

It is now well established that seasonal reproduction in sheep is to the result of a pronounced seasonal shift in the hypothalamic responsiveness to oestradiol, which alternates a negative-feedback effect during the sexual rest period and a positive-feedback effect during the breeding season (Legan et al., 1977; Goodman et al., 1982; Platt et al., 1983). During the seasonal anoestrus under long days exposure, the intensity of the oestradiol negative feedback on LH secretion increases, which leads to a decrease in the pulsatile release of GnRH and thus to the interruption of ovulation (Legan et al., 1977; Goodman et al., 1982; Martin et al., 1983; Viguie et al., 1995). Neurons that express kisspeptin (Kiss) a major modulator of reproductive function in mammals may be involved in the oestrogen-dependent regulation of GnRH and LH secretion in the ewe, which has been suggested by the distribution pattern of Kiss immunoreactivity in the hypothalamus. In the mammalian hypothalamus, Kiss-expressing neurons are detected in two main neuronal populations, including one population scattered through the pre-optic area (POA) and the other population located in the arcuate nucleus (ARC). In sheep, half of the Kiss-expressing neurons in the POA and approximately all Kiss-expressing neurons in the ARC express the estrogen receptor-α (ER-α) (Franceschini et al., 2006; Smith et al., 2005a). In non-seasonal rodent, Kiss-expressing neurons of the anteroventral periventricular nucleus (AVPV), which all express oestrogen receptor ER-α (Smith et al., 2005a), convey the oestrogen positive feedback to GnRH neurons (Smith et al., 2005a, 2005b). Whereas the physiological function of Kiss-expressing neurons located in the ovine POA remains unsolved, Kiss-expressing neurons that reside the caudal ARC may mediate the positive feedback of oestradiol during the preovulatory period (Estrada et al., 2006). In addition, sex steroids regulate Kiss-expressing neurons in the sheep ARC (Smith et al., 2007), as well as the mouse ARC (Smith et al., 2005a, 2005b). In this region, Kiss expression is also regulated by the photoperiod, independently of sex steroids (Smith and Clarke, 2010; Simonneaux et al., 2012; Smith, 2012). Thus, data in hamsters and sheep support a role for kisspeptin neurons from the ARC in the control of seasonal reproduction and suggest that a single melatonin message can produce opposite reproductive responses depending on whether short- or long-day breeders are concerned.

2.2. Metabolic regulation in seasonal mammals

Comparable to what is observed for reproductive activity, most species that inhabite temperate and arctic latitudes, exhibit robust annual cyclic variations in body weight, which are triggered by changes in the photoperiod (review in Bartness et al. (2002)). Extensive investigations have firmly established the hypothalamus as the major homeostatic structure that controls whole-body energy balance (Anand and Brobeck, 1951, review in Elmquist et al. (1999)).

In sheep, hypothalamic neuropeptides including neuropeptide Y, agouti-related protein (AGRP) and orexin, play key roles in appetite regulation and their expression is modulated by the photoperiod, which suggests their putative involvement in the seasonal control of food intake and body weight regulation (Archer et al., 2002; Clarke et al., 2003). In addition, the destruction of the ARC impedes both the photoperiodic and homeostatic control of food intake and body weight (Lincoln et al., 2001) and intrahypothalamic administrations of melatonin, in animals exposed to a long photoperiod induce a shift in the phase of the body weight cycle (Lincoln and Maeda, 1992). Collectively, these data suggest a role of the medio-basal hypothalamus in the seasonal control of food intake and body weight in sheep.

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