Environmental and neuroendocrine control of breeding activity in the dromedary camel

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Abstract

The dromedary camel (*Camelus dromedarius*), a well-adapted desert mammal, is a seasonal breeder whose sexual activity occurs during the winter and spring. These periods coincide with food resources and climate conditions are favorable for offspring's survival. The mechanisms involved in the control of this seasonality however still need to be elucidated. The aim of this review is to describe the reproductive patterns of the dromedary camel. This includes the geographical seasonal breeding distribution of this species taking into account the role of various physical environmental parameters notably temperature, day length and the amount of rainfall. Further, various aspects of seasonal breeding in male and female camels are discussed as well as the neuroendocrine factors that may control seasonal such phenomena. Finally, the putative roles of two hypothalamic neuropeptides, kisspeptin and (Arg) (Phe) related peptide, are proposed for the control of camel's seasonal reproduction.

Keywords: Dromedary camel, seasonal breeding, rainfall, photoperiod, ambient temperature, food availability, Kisspeptin, RFRP

Le contrôle environnemental et neuroendocrinien de l'activité saisonnière de la reproduction chez le dromadaire

Résumé

Le dromadaire (*Camelus dromedarius*), qui est un mammifère bien adapté au désert est une espèce à reproduction saisonnière. Sa saison sexuelle a lieu durant l'hiver et le printemps. Ces périodes coïncident avec l'abondance des ressources alimentaires et des conditions climatiques favorables pour la survie de la progéniture. Toutefois les mécanismes impliqués dans le contrôle de cette saisonnalité restent encore mal élucidés. L'objectif de cette revue est de décrire les caractéristiques de la reproduction chez le dromadaire. Cela inclue la distribution géographique de sa saison sexuelle et son déclenchement possible par plusieurs paramètres environnementaux physiques, notamment la température ambiante, la photopériode et la quantité de précipitations. De plus, plusieurs aspects de cette saisonnalité ont été discutés chez le mâle et la femelle. Finalement, cette revue analyse les facteurs neuroendocriniens impliqués dans la saisonnalité de reproduction, notamment, le rôle putatif de deux neuropeptides hypothalamiques, le kisspeptin et le (Arg) (Phe) peptide apparenté.

Mots-clés: Dromadaire, saisonnalité de reproduction, précipitations, photopériode, température ambiante, disponibilité alimentaire, kisspeptin, RFRP.

INTRODUCTION

All living organisms have to adapt their physiological processes to the daily and seasonal environmental changes of their biotopes. Various functions such migration, hibernation, molting, diapause and reproduction are adjusted to occur in an adequate period of the year. Notably, a tight timing of reproduction is crucial for optimizing birthing and survival of the offspring. This control involves the effect of genetic, metabolic and environmental factors. Seasonal breeding species are grouped into "long day" and "short day" breeders depending on time of the year when mating activity occurs. "Long day" breeders become sexually active when day length gets longer (spring-summer); while in "short day" breeders this activity arises when day length goes shorter. Furthermore, reproductive capacity depends on climatic conditions. Thus, animals living under harsh environmental conditions must cope with their biotopes and need to better synchronize their reproductive activity.

The dromedary camel is a well-adapted desert mammal. It displays a large distribution including three continents within a latitudinal zone laying between 40°N to 40°S (Figure 1). The distribution area is mainly confined to the semi-arid and arid regions of Africa and Asia. More than 80% of the world camel's population is found in Africa particularly North Africa, Sahel and the Horn of Africa. In Asia, a regular camel population is found in India and Pakistan, in addition to Arabian countries. Finally, an important population of camel is also found in Australia. This species exhibit a seasonal reproduction with mating-induced ovulation. Its breeding season is relatively short and the gestation period lasts 13 months. This period may be affected by the date of conception (Elias *et al*., 1991) food availability (Yagil and Etzion, 1984). Therefore, mating and parturition are

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occurring at the same period of the year which depends on camel's geographical distribution. In most cases, the matting period occurs during the rainfall period associated with low ambient temperatures and good food availability. Several studies have been carried out in different Asian and African countries to define the breeding season in the camel and the environmental factors which may determine its onset and its end. Photoperiod, ambient temperature and rainfall with subsequent food availability seem to be the three major abiotic factors that have been considered to be involved in this seasonality. The exact role of each of these abiotic factors in the control of reproduction seasonality in camels requires a thorough analysis.

Understanding the mechanisms through which rhythmic changes of environmental factors restrain camel's breeding activity to a definite period of the year is critical for advancing knowledge of reproductive physiology and breeding management. In most seasonal mammals, the annual changes in the nocturnal production of melatonin is pivotal to drive seasonal breeding. Recent studies have provided evidences that melatonin is involved in the regulation of two populations (kisspeptin (Kp) or (Arg)(Phe)-related peptide (RFRP)) of hypothalamic neuropeptides involved in the control of GnRH neuronal activity and the downstream pituitary-gonadal axis (Clarkson and Herbison, 2006; Irwig *et al.,* 2004; Kriegsfeld *et al.,* 2006; Rizwan *et al.*, 2012).

The objective of the present review is to provide a new and thorough look at camel reproductive seasonality, firstly through reviewing the role of abiotic factors in the control of seasonal breeding in camels distributed within 16 geographical zones (latitudinal distribution between 33°N to 40°S) and secondly by investigating how the different environmental cues impact on the neuroendocrine control of seasonal breeding with a special focus on the putative role of Kp and RFRP neurons.

BEHAVIOR, GONADAL AND HORMONAL CHANGES DURING THE CAMEL'S BREEDING CYCLES

In male, the breeding season is characterized by several changes in sexual behavior including aggressiveness, exteriorization of the soft palate, urine spraying and smudging of poll gland secretions (Tibary and Anouassi, 1997). During this period, the testes and accessory glands show large increase in size, weight and activity (Abdel-Raouf *et al.*, 1975; Sigh and Bharadwaj, 1978; Yagil and Etzion, 1980). The seminiferous tubule's diameter becomes larger during the breeding season (Abdel-Raouf *et al.*, 1975). The accessory gland weight increase in parallel with the testis indicating that their activity is regulated by androgens (Mahmoud, 2006). Recently, S-100 and alpha smooth muscle actin, two biologically active proteins of the epididymis, have been reported to exhibit seasonal changes with a higher expression at the breeding season (Ibrahim *et al.*, 2016).

Although spermatogenesis and male hormone (testosterone and progesterone) secretion occur continuously throughout the year, both are higher during the breeding season (Tingari *et al.*, 1984, Abdel-Raouf *et al.*, 1975; Zia-ur-Rahman *et al.*, 2007; Bedrak *et al.*, 1983; El-Harairy and Attia, 2010). The seasonal regulation of androgen secretion is linked to changes in pituitary activity since luteinizing hormone (LH) secretion shows higher frequency and amplitude during rutting (Marie, 1987) while FSH levels are higher when ambient temperature is low (Fat-Halla and Ismail, 1980). In addition, serum prolactin levels are also higher during the non-breeding season and decrease significantly in the rutting season (Ismail *et al.*, 1984; Azouz *et al.*, 1992).

In female camel, a number of behavioral changes are observed during the breeding season such as frequent urination, vulvae discharge, vulvae swelling, male seeking, bleating, foul vulval odor, tail raising, inappetence and mounting behavior (Tibary and Anouassi, 1997; Abdussamad *et al.*, 2011). Female dromedaries are seasonal polyestrous animals with a sustained ovarian follicular cycle in the breading season until fecundation. In the non-breading season, ovarian activity decreases down to a limited number of small follicles (Sghiri and Driancourt, 1999).

Estradiol levels follow the ovarian activity with higher cycling levels in the breeding season and low levels during the non-breeding season (Elias *et al.*, 1984; Ali *et al.*, 2007). In correlation with the ovaries, pituitary activity attested by LH secretion, is lower in summer than in winter (Khaldoun, 1990). Furthermore, pituitary's sensitivity to GnRH is increased during the rutting season, with a larger release of LH (Bono *et al.*, 1989).

TIMING OF THE BREEDING SEASON AROUND THE WORLD

Because camel reproductive activity strongly depends on environmental factors, the timing of their breeding varies according to geographical location (Table 1).

Analysis of camel's breeding seasons in 16 zoogeographical zones distributed from latitude 33°N to 40°S, may help understanding the involvement of photoperiod,

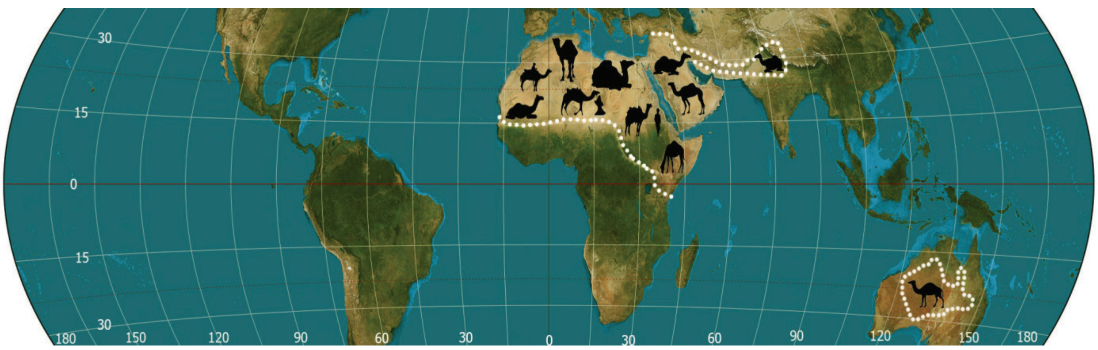

Figure 1: Zoogeographical distribution of dromedary camel in the world

ambient temperature and rainfall with subsequent food availability in the triggering of breeding activity (Figures 2 and 3).

At high latitude (from 33°N to 23°N), in Algeria, Egypt, India, Israel, Morocco, Oman, Pakistan, Saudi Arabia, Tunisia, and UAE, the breeding season occurs under short photoperiod associated with rainfall and low ambient temperatures.

In Mali (latitude 16°N), the breeding season takes place during the short days but its onset occurs earlier after the summer solstice. This may be related to the abundance of rainfall and thus good food availability at this period.

More towards the south, in Nigeria (latitude 12°N) the breeding season is limited to short days whereas in Sudan (latitude 14°N) it extends to several months in long days. In these geographical zones, temperature and photoperiod profiles are similar and the rainfall occurs at the same period although the amount of rainfall is usually higher in Nigeria (240 mm) than in Sudan (110 mm). The climatic conditions are more drastic in Sudan and therefore camel's reproductive cycle is well synchronized to the rainfall period. A prediction of this rainfall period triggers the reproductive activity to start early than in Nigeria and to extend the breeding season beyond the precipitation period. In Nigeria, the precipitation rate during a single period of the year maintains food availability during the following months, and thus the breeding season is rather driven by short photoperiod and low ambient temperatures that rainfall as in the case in zones of high latitudes.

In Somalia (latitude 3°N), ambient temperature and photoperiod are nearly constant throughout the year but precipitations occur at two seasons. The two breeding seasons in this area correspond to the two rainy seasons because of food abundance.

In Kenya (latitude 0°), photoperiod, ambient temperature are constant and precipitation occurs almost all the months and consequently, food availability and climatic conditions are quite stable throughout the year. Therefore, although camels are able to integrate environmental changes, seasonal reproduction is not required and camel can breed at any period of the year. In fact, very small changes in the environment can be perceived by animals. As an example, it was demonstrated that the *Arvicanthis niloticus* a small tropical rodent is able to integrate minimal annual variations of photoperiod which can arrive at 45 min of differences (Sicard *et al*., 1992).

In Australia (latitude 23 °S) camel's breeding season also occur under short photoperiod and low ambient temperatures, and therefore its timing shows a six-months out of phase when compared to that in northern hemisphere. Photoperiod and temperature appear the most relevant cues since rainfall occurs with a low rate throughout the year.

As a general rule, the breeding season in the dromedary camel living at high latitudes of both northern and southern hemispheres occurs when the photoperiod is short and the temperature is low associated to some precipitations. Therefore, their reproductive cycle is in opposite phase relationship between the both hemispheres, as for other mammals like ewes in which the breeding season starts when day length decreases (end of summer/beginning of autumn) in the northern hemisphere, and when day length increases in the southern hemisphere (for review see Lofts, 1975; Vivien-Roels and Pévet, 1983). At high latitudes, annual cycles of photoperiod and probably ambient temperature are strong enough to synchronize reproductive activity to rainfall and good food availability period. However, when climatic conditions are drastic with limited rainfall, the breeding season tends to start earlier during long days or may also appears twice a year to match precisely the two rainfall seasons. There is no need to compare rainfall and food availability to photoperiod and ambient temperature, since the later are proximate factors while the former are ultimate factors (Lofts, 1975; Gwinner, 1981). An interesting case is observed in Sudan where the breeding season starts earlier than the rainfall season indicating the existence of a predictive adaptation. In the equatorial area also, camel can breed throughout the year as rainfall and good food availability are quite stable all along the year.

Table 1: Breeding season of dromedary camel in different countries

Country / Region	Breeding season	References
Tunisia	November-March	Moslam and Megdiche, 1989; Fatnassi *et al*., 2016
Algeria	November-March	Mayouf *et al*., 2014; Gherissi *et al*., 2016; Benaissa *et al*., 2016
Pakistan	November-April	Ali *et al*., 2007; Yasin and Wahid, 1957; Zia-ur-Rahman, 2007
Israel	December-April	Elias *et al*., 1985; Bedrak *et al*., 1983; Yagil and Etzion, 1980
India	December-March	Khanna *et al*., 1990
Egypt	December-April	Abdoun, 2001; El-Harairy and Attia, 2010
Morocco	November-April	Sghiri and Driancourt, 1999; Tibary and Anouassi, 1997
United Arab Emirates	October-March/April	Tibary and Anouassi, 1997
Saudi Arabia	November-April	Al-Qarawi *et al*., 2001
Oman	December-March	Manjunatha *et al*., 2015
Mali	July-January	Traoré *et al*., 2014
Sudan	May-August	Abbas *et al*., 1992 ; Ibrahim, 2016; Babiker *et al.,* 2011
Nigeria	October-December	Abdussamad *et al*., 2011
Somalia	April-June October-December	Elmi, 1989
Kenya	Throughout the year	Wilson, 1986
Australia	June-September	McKnight, 1969

INVOLVEMENT OF FOOD AVAILABILITY, AMBIENT TEMPERATURE AND PHOTOPERIOD CYCLES IN THE ONSET OF CAMEL BREEDING SEASON

Several studies have been conducted on the behavioral and hormonal control of reproduction in the dromedary camel. However, only a few works have investigated the effect of environmental factors on their breeding seasonality.

Food availability and energy balance

Energy given by food intake is used for different metabolic processes or stored as glycogen or lipids in the body. Basic metabolism, necessary for homeostasis, should be first satisfied, while other functions of high energetic cost, such as growth and reproduction, can be satisfied later on in the case of negative energy balance (Bronson, 2009). Indeed, food availability is the ultimate factor for the survival of the offspring (Lofts, 1975; Gwinner, 1981).

As stated above, breeding activity in the camel is usually synchronized with the rainfall periods so that birth of offspring occurs during a good grazing period. It seems that rainfall cue can partially or totally override the effect of photoperiod (Musa *et al*., 1993; Mukasa-Mugerwa, 1981). Indeed, in the United Arab Emirates, it was reported that well-fed and watered female camels maintain their ovarian activity throughout the year and that the seasonal aspect of the breeding in this species was rather linked to the increased embryonic loss and decreased libido of males during summer season (Tibary and Anouassi, 1997). It has been also demonstrated, that rainfall season can affect ovarian activity and gonadotropin secretion, with

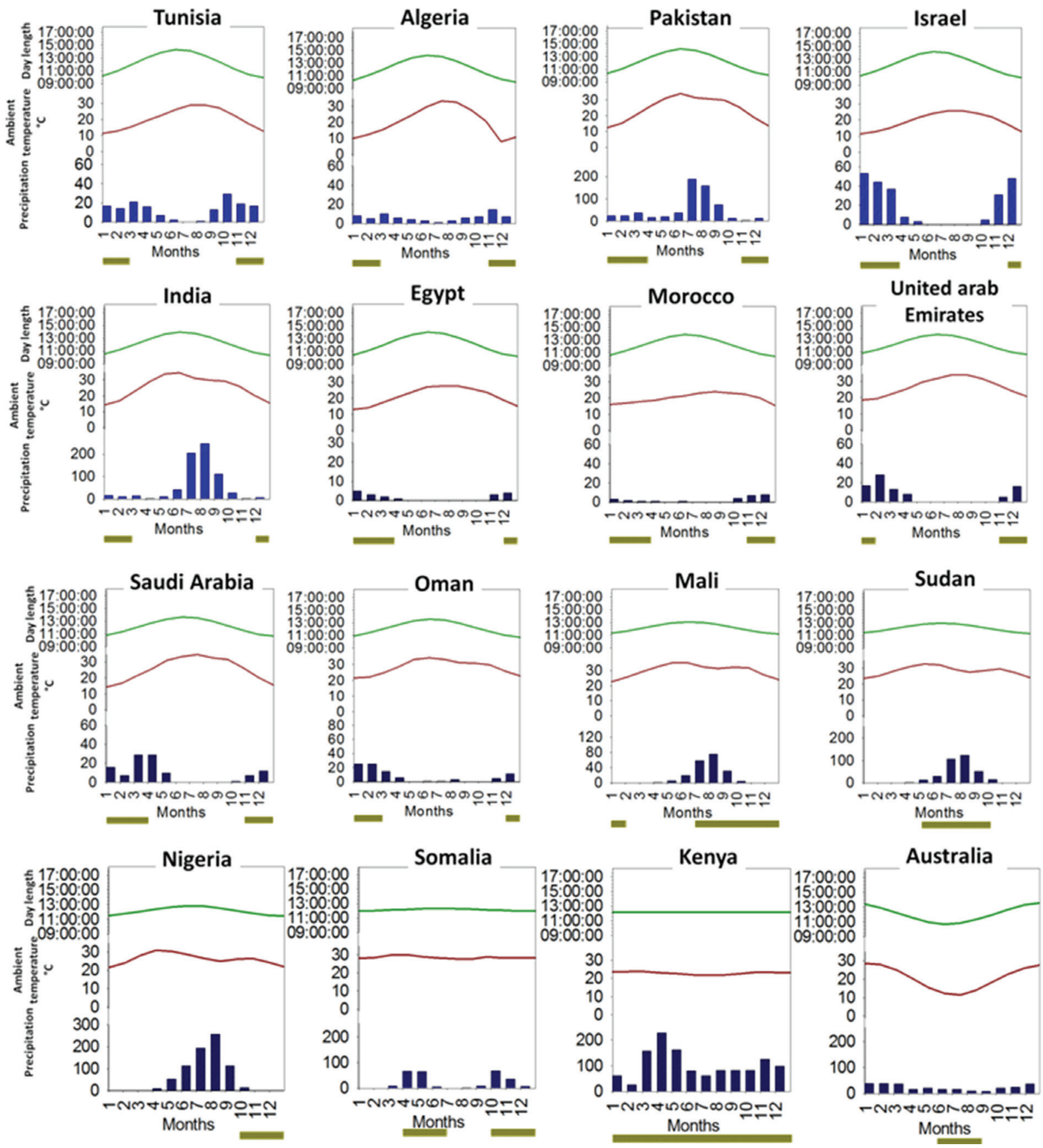

Figure 2: Representations of the breeding season (indicated by the green bar below each panel) as a function of the photoperiod (green curve), ambient temperature (brown curve) and rainfall (histograms). The period of breeding season was obtained from literature as given in Table 1. At each location, photoperiod data were obtained from the website http://otaff.ca/soleil/?lang=en_CA; while that of ambient temperature and precipitation were from the website http://fr.climate-data.org

higher GnRH responsiveness, LH and sex steroid secretion during this season (Bono *et al*., 1989; Bono *et al*., 1988). However, these changes cannot be attributed to a direct effect of precipitation, but possibly to a synergism with photoperiod and ambient temperature since all these cues show seasonal variations. Because photoperiod and ambient temperature show the most predictable annual changes, camels probably use these cues to predict the suitable climate for breeding. At our knowledge, there are no controlled experimental designs that permits discriminating an unique effect of one single environmental factor in camels. In the equatorial countries, such as Kenya, there is sufficient food available all along the year and therefore camel breed at any time of the year.

An equilibrated body energy balance, reached when the amount of food intake is sufficient to counteract energy cost, is crucial to sustain reproductive activity. In most female mammal, including farm animals, food restriction is known to impede ovarian activity (Comin *et al* 2002; Li *et al*., 2014) Thus, in food restricted mice, ovulation is abolished until they can increase their food intake, even if they are kept at low temperatures (Manning et Bronson, 1990). Similarly, it has been shown that low circulating level of glucose or metabolic inhibition reduces GnRH neurons activity (Zhang *et al*., 2007).

In order to elucidate how metabolic cues control of reproduction, several studies focused on kisspeptin (Kp), a hypothalamic peptide essential for puberty onset and normal reproduction (De Roux *et al*., 2003; Seminara *et al*., 2003). Kp is a product of the *Kiss1* gene expressed in neurons of the arcuate nuclei or in more rostral areas around the third ventricle (anteroventral paraventricular nucleus in rodents, or preoptic area in larger mammals). Kp is an extremely potent stimulator of GnRH neuronal activity and consequently gonadotropin secretion (Clarke *et al*., 2008). There is evidence of a relationship between

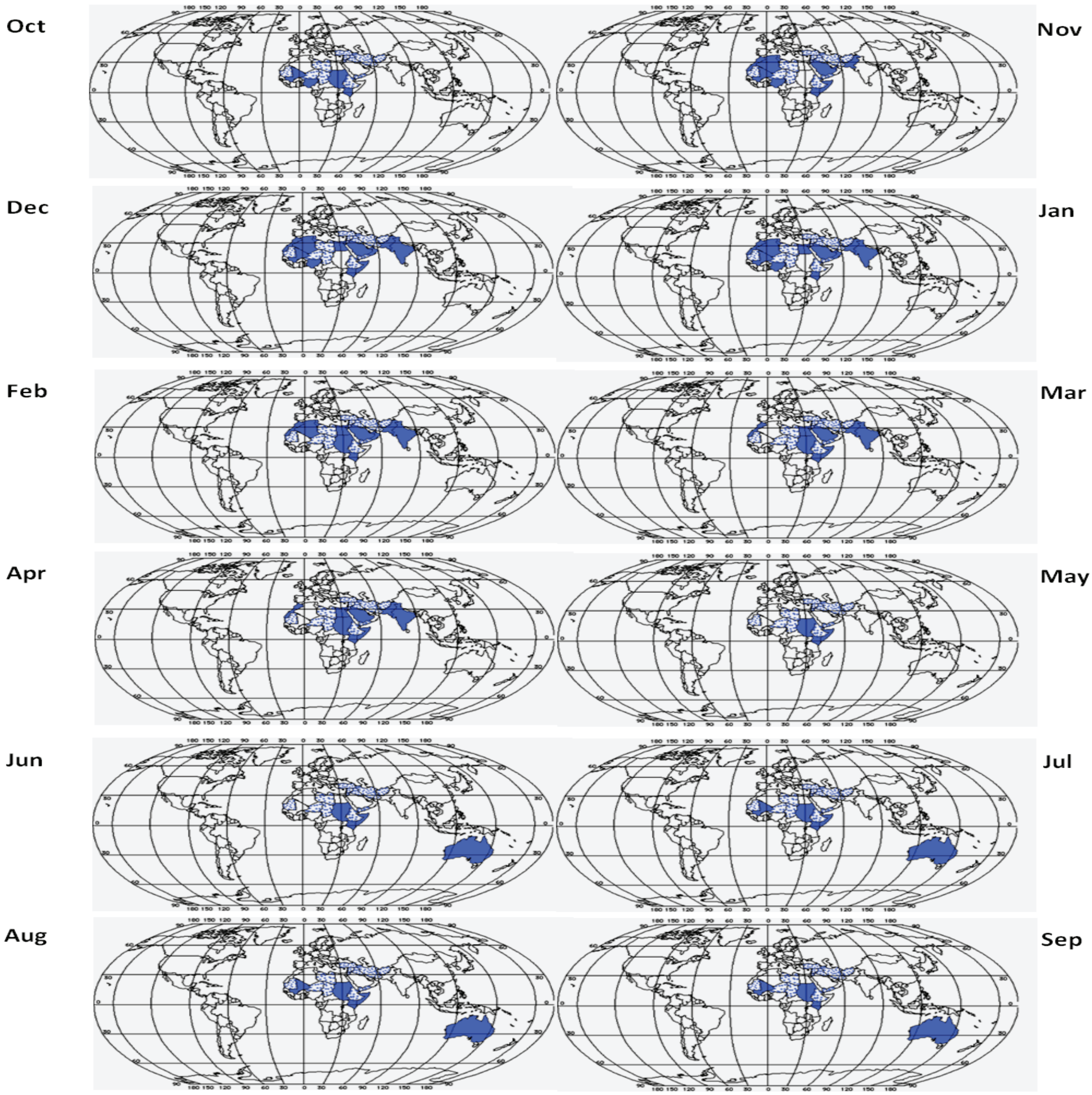

Figure 3: Camel seasonal breeding distribution around the world throughout the year (blue color). Dashed areas represent other countries where dromedary camel is present but its breeding season is not reported in literature

the metabolic status and kisspeptin expression. For example, fasting in rat induces a decrease in Kp expression associated with an increase in its G protein-coupled receptor Kiss1R (Castellano *et al*., 2005). In line with this, Kp neurons in the arcuate nucleus express the receptor for leptin, an anorexigenic hormone produced by fatty tissues (Margetic *et al*., 2002). Additionally, administration of this hormone to leptin knock-out mice restores Kp expression to a level comparable to that observed in the wild type animals (Smith *et al*., 2006). Other metabolic modulators, like ghrelin, proopiomelanocortin (POMC) and neuropeptide Y (NPY) are possible regulators of Kp neurons (De Bond and Smith, 2014). These observations suggest that Kp neurons may be able to adjust the activity of the gonadotropic axis according to the metabolic state of the body (De Bond and Smith, 2014; Garcia-Garcia, 2012).

Effect of ambient temperature on breeding activity

Arid and semi-arid areas display variations in photoperiod but also exhibit high fluctuations of ambient temperature. In mammals, extreme temperatures can induce irregularities in sexual activity like delayed puberty, delayed onset of breeding season, irregular cycle duration and frequent anovulatory estrus (Hafez, 1964). In sheep, the strongest regulator of seasonal breeding is photoperiod but ambient temperature may also modulate this activity (Rosa et Bryant, 2003). Ewes are short day breeder at high latitudes and long day breeder at low latitude, but it was reported that when ewes from northern hemisphere were put under low ambient temperatures during the summer, their reproductive season began earlier than those kept under normal temperatures (Dutt and Bush, 1955; Godley *et al.*, 1966). In goats, heat stress induces a decrease of ovary LH receptor and responsiveness to LH pulses, a decrease in follicular steroidogenic activity attested by a reduction in oestradiol synthesis and a delay in recruitment of the ovulatory follicle (Kanai *et al*., 1995; Ozawa *et al*., 2005). In mares, high temperature was associated with disturbance of the estrous cycle, development of anovulatory hemorrhagic follicles and increased early embryo loss. In cattle, high ambient temperature and humidity (heat index) affect not only steroidogenesis but also quality of oocytes and results in poor fertility and increased pregnancy loss (Ana Yasha *et al*., 2017; Hansen, 2009).

One of the pineal hormones, 5-methoxytryptophol (5ML) was proposed to act as mediator for the effect of ambient temperature on reproduction. Indeed, as reviewed by Vivien-Roels and Pévet (1983), ambient temperature affects pineal gland activity in different vertebrates including mammals. In the jerboa, 5ML levels are lower during the breeding seasons (spring) and injection of this pineal hormone induces a decrease in testicular volume (Bouhaddou, 2016). In the dromedary camel, except the losing weight effect (up to 30%) observed in males during the breeding period (Anouassi and Tibary, clinical observations), there is no report evoking a direct effect of ambient temperature on its reproductive activity. However, a recent study performed in our laboratory has reported that in the camel the ambient temperature cycles drive melatonin rhythm as does photoperiod (El Allali *et al*., 2013). This indicates that a thermo-period related to the annual cycles of ambient temperature can also synchronize the breeding season in camel.

Control of seasonal breeding by photoperiod

Photoperiod is the major environmental factor synchronizing seasonal reproduction as reviewed in several species (Reiter, 1978; 1981; 1974; Hoffman, 1979; Lincoln, 1979; 1992; Lincoln and Short, 1980; Lincoln and Richardson, 1998; Lincoln *et al*., 2001). Artificial modification of the photoperiod (lighting conditions) is used to advance the breeding season in goat and sheep (Malpaux *et al*., 1999) and horses (Murphy *et al*., 2014).

Animals are informed about annual variations in photoperiod through changes in the duration of the melatonin nocturnal peak (Bartness *et al.*, 1993; Goldman, 2001). Melatonin synthesis and release from the pineal gland depend on a neuronal pathway involving a retino-hypothalamic tract connecting the retina to the hypothalamic suprachiasmatic nuclei which host the master circadian clock and downstream the hypothalamic paraventricular nuclei, the intermediolateral cell column of spinal cord and the superior cervical ganglia which noradrenergic neurons project to the pineal gland (Larsen *et al*., 1998; Teclemariam-Mesbah *et al*., 1999). The release of norepinephrine occurs at night only under the control of the circadian clock synchronized by the light/dark cycle perceived by the retina (Drijfhout *et al*., 1996). Norepinephrine displays a potent stimulatory effect on melatonin synthesis (King and Steinlechner, 1985; Stehle *et al*., 2001). Therefore, circulating melatonin is about 10 times higher during the

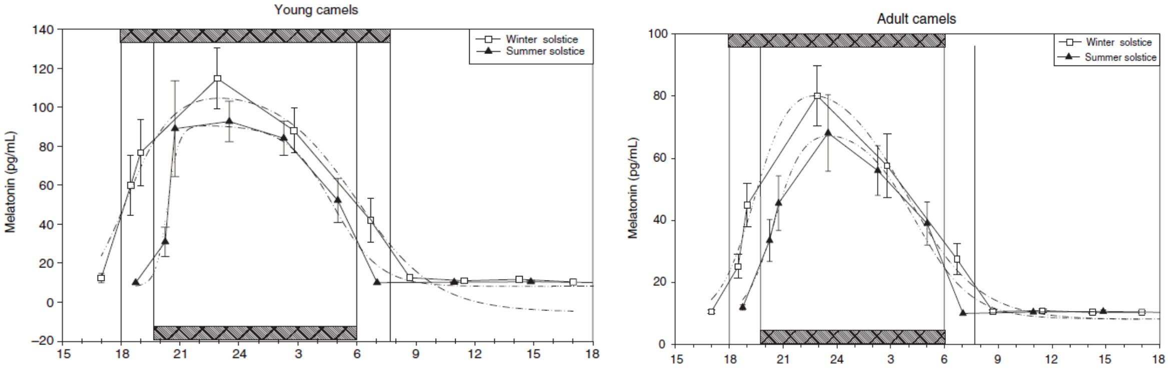

Figure 4: Seasonal variations in the daily rhythm of circulating melatonin in young and adult camels during the two solstices. The shaded bars indicate the night periods. Values are expressed as mean ± SEM of 6 young and 11 adult camels. (El Allali et al., 2005)

night and the duration of the nocturnal melatonin peak is proportional to the duration of the night (Illnerova *et al*., 1984; Arendt, 1986; Reiter, 1986; Pévet *et al*., 1991; Reitter, 1993; Tast *et al*., 2001).

Like other mammals, the dromedary camel shows daily (Vyas *et al*., 1997) and seasonal (El Allali *et al*., 2005) rhythms in melatonin. Indeed, this species, integrates photoperiodic changes under various latitudes through changes in the duration of the nocturnal melatonin peak (Figure 4). Therefore, camels may use the photoperiodic change in melatonin synthesis to synchronize their breeding season.

Recent research findings are in favor of a melatonin effect on the breeding season in the camel. An early experiment carried out by Vyas *et al*., (2008) revealed that application of a short photoperiod treatment by protecting the eyes from the solar lights stimulates the ovarian activity in sexually quiescent female camels. Later, Dholpuria *et al*., (2012) showed that during the breeding season, melatonin implant improved fertility by increasing follicular growth. Similarly, in a recent study we observed that exogenous melatonin given during the seasonal anestrus period increased the ovarian activity of 6 camels as compared to a control group (El Allali, unpublished data). In male camels, melatonin implants can improve reproductive performance during the non-breeding season by increasing libido and testosterone levels in the treated camels as compared to the controls (Swelum *et al*., 2016)

In all seasonal mammals studied so far, photoperiodic variations of the nocturnal peak of melatonin synchronize reproduction activity with the season. In several species, exogenous melatonin was used to control the season of breeding and increase fertility and prolificacy (Bartness *et al*., 1993; Misztal *et al*., 2002). Melatonin acts via its specific receptors MT1 (Mel1a), MT2 (Mel1b) which are expressed in multiple tissues through the body (Dufourny *et al*., 2008; Reppert *et al.*, 1996) with the highest concentration of MT1 observed in the *pars tuberalis* (PT) of numerous species (Vaněcek *et al*., 1987; Weaver *et al*., 1989; Williams *et al*., 1989).

PT integration of melatonin signal via the MT1 receptors results in the regulation of thyroid-stimulating hormone (TSH) synthesis with at much higher levels in long photoperiod as compared to short photoperiod (Dardente *et al*., 2012). TSH then activates tanycytes TSH receptor to increase thyroid hormone (T3) levels in the mediobasal hypothalamus via a dual activation of deiodinases 2 and inhibition of deiodinases 3 (Dardente, 2012; Hanon *et al*., 2010; Klosen *et al*., 2013; Nakao *et al*., 2008). Recently, Klosen *et al.,* (2013) have shown that chronic administration of TSH to sexually inhibited short photoperiod adapted Siberian and Syrian male hamsters, restores a long day reproductive phenotype. In parallel, TSH could increase the expression of two neuropeptides recently described to be involved, in the control of seasonal breeding, the hypothalamic RFRP and Kp peptides (Revel *et al*., 2006; Ancel *et al*., 2012). These results lead to the hypothesis that the control of seasonal breeding by the melatonin-TSH-T3 occurs via these neurons (Klosen *et al*., 2013; Dardente *et al*., 2016) (Figure 5).

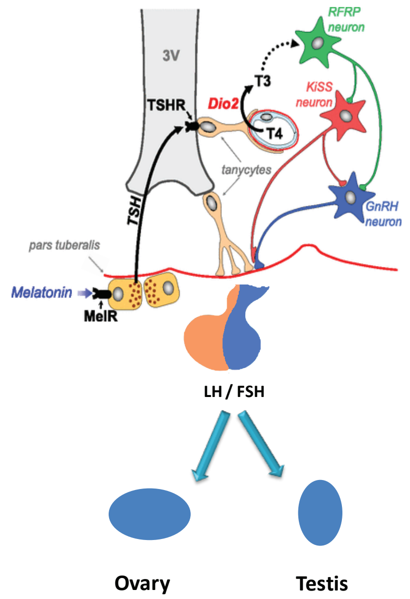

Figure 5: Schematic illustration showing how melatonin controls the seasonal breeding. By acting on the pars tuberalis, low levels of melatonin during long days allows high thyroid stimulating hormone (TSH) production, which increases deiodinase 2 (Dio2) expression in the tanycytes lining the 3rd ventricle leading to a local increase of T3 production. T3 is thought to increase the synthesis of kisspeptin (KISS) and (ARG)(PHE)related peptide (RFRP), two neuropeptides involved in the regulation GnRH neurons and the downstream secretion of two pituitary hormones, LH and FSH , that regulate gonad activity (modified from Klosen et al., 2013)

KISSPEPTIN SYSTEM AND SEASONAL REPRODUCTION

The *Kiss1* gene was first discovered in 1996 as an inhibitor of human melanoma metastatic potential (Lee *et al*., 1996). The *Kiss1* gene is translated into a long propeptide of 145 amino acids (aa) which is further cleaved into shorter peptides with sequences varying from 10 to 54 aa (Kotani *et al*., 2001; Ohtaki *et al*., 2001). All Kp isoforms contain the minimal 10 aa N-terminal active sequence allowing their binding to the 7 transmembrane domains G protein coupled receptor, Kiss1R (previously named GPR54) (Kotani *et al*., 2001; Muir *et al*., 2001; Ohtaki *et al*., 2001). Kiss1R are highly expressed on GnRH neurons and their activation is responsible for the stimulation the reproductive axis (Clarkson and Herbison, 2006).

In several mammalian species, a cluster of Kp neurons is found in the arcuate nucleus (ARC) (Rat, Irwig *et al*., 2004; Desroziers *et al*., 2010; Sheep, Estrada *et al*., 2006; Goodman *et al*., 2007; Hamster, Revel *et al*., 2006; Mason *et al*., 2007; Mouse, Clarkson et Herbison, 2006; Primates, Rometo *et al*., 2007; Ramaswamy *et al*., 2008; Hrabovszky *et al*., 2010; Equine, Decourt *et al*., 2008 Magee *et al*., 2009). In addition, Kp neurons are identified in the pre-optic region in human, monkey, sheep, and rodents. In rodent, these neurons are located in the anteroventral periventricular nucleus (AVPV) and extend to the periventricular nucleus (PeN) (Gottsch *et al*., 2004; Smith *et al*., 2005); whereas in sheep, monkey and man, they extend rostro-caudally to reach the pre-optic area (POA) (Lehman *et al*., 2014). Notably, these two neuronal populations exhibit sexual dimorphism in most of the species studied to date. In sheep and human, ARC and POA Kp are more numerous in females than in males (Cheng *et al.*, 2010; Hrabovszky *et al.*, 2010); whereas in rodents only the AVPV shows higher Kp neurons in females than in males (Clarkson and Herbison, 2006; Kauffman *et al.*, 2007).

Revel *et al.,* (2006) demonstrated in Syrian hamsters that the *Kiss1* gene expression is inhibited by melatonin in short photoperiod, and that this melatonin-driven expression of *Kiss1* plays a pivotal role in the seasonal control of the gonadotropic axis. Further studies in sheep also reported strong photoperiodic variation of *Kiss1* expression (Wagner *et al.*, 2008; Smith *et al.*, 2007; Chalivoix *et al.*, 2010; Figure 6). Importantly *Kiss1* expression is strongly regulated by sex steroid feedback but this effect is opposite in the ARC (inhibition of *Kiss1* expression) and AVPV/POA (stimulation of *Kiss1* expression) (Smith *et al.*, 2005; Ansel *et al.*, 2010). There is an opposite regulation of the ARC *Kiss1* gene, with higher levels during short photoperiod in sheep and during long photoperiod in Syrian hamster, in conjunction with seasonal reproductive activity. Photoperiod also affects the density of Kp fibers projections onto GnRH neurons (Smith *et al.*, 2008).

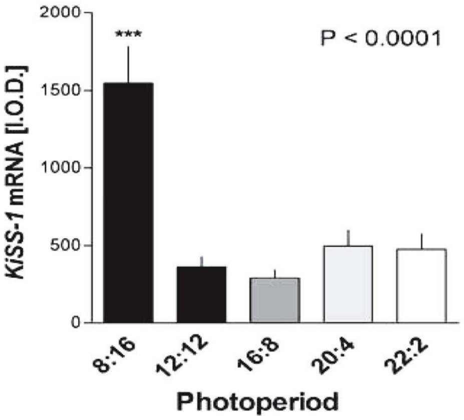

Figure 6: Photoperiod effect on Kiss-1 expression in the sheep arcuate nuclei (Wagner et al., 2008)

In both hamster (Revel *et al.*, 2006) and ewe (Caraty *et al.*, 2010), chronic administration of Kp to sexually inactive animals restores gonadal activity to the level observed during the breeding season. This demonstrates that seasonal regulation of Kp is pivotal to synchronization of reproduction with seasons. In camel, preliminary results in our laboratory (Ainani, El Bousmaki, Achaâban, Ouassat, Piro, Simonneaux and El Allali, unpublished data) show that Kp is expressed in neurons in the various hypothalamic nuclei. Further studies are needed to establish whether this neuropeptide may be involved in camel seasonal breeding (Figure 7).

RFRP SYSTEM AND SEASONAL REPRODUCTION

RFRP peptides are hypothalamic peptides belonging to the same RFamide peptide family as does Kp. A homologous peptide called gonadotrophin inhibitory hormone (GnIH) has first been discovered in the quail to inhibit GnRH-induced LH release by the pituitary (Hinuma *et al.*, 2000). In mammals, the orthologous gene is called *Rfrp* and encodes three peptides RFRP-1,-2 and 3 peptides. Only RFRP-1 and RFRP-3 are found in rodents (Fukusumi *et al.*, 2001; Ukena *et al.*, 2002). In all species investigated thus far, the RFRP neurons are located in an area between DMH and VMH (Hinuma *et al.*, 2000; Revel et *al.*, 2008; Clarke *et al.*, 2008; Dardente *et al.*, 2008; Henningsen *et al.*, 2016) (Figure 8).

As Kp neurons, RFRP neurons display a marked photoperiodic variation. However, unlike Kp, this photoperiodic variation is driven by melatonin only. It is not controlled by sex steroid feedback and is inhibited during the short photoperiod in all seasonal species investigated (Revel *et al.*, 2008; Dardente *et al.*, 2008; Clarke *et al.*, 2008; Ancel *et al.*, 2012; Ubuka *et al.*, 2012; Janati *et al.*, 2013; Talbi *et al.*, 2016; Henningsen *et al.*, 2016) (Figure 8). In the Syrian hamster, the number of RFRP neurons is higher in females than in males (Henningsen *et al.*, 2016; Figure 8).

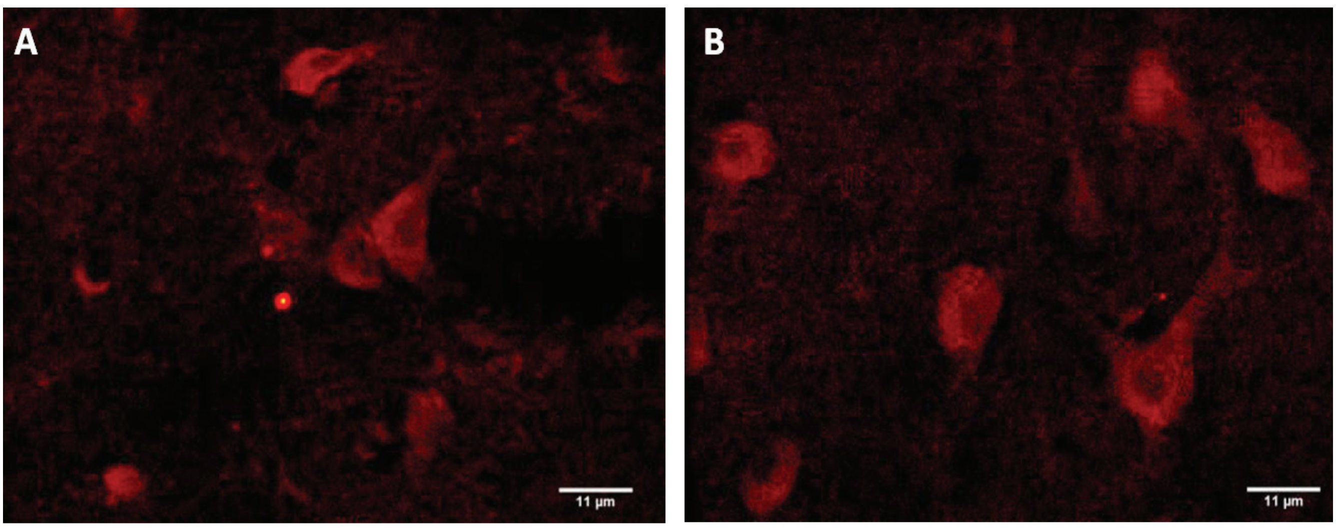

Figure 7: Immunofluorescent labeling of kisspeptin neurons in (A) the pre-optic area (POA) and (B) arcuate nucleus (Arc) of female camel

Although RFRP has often been reported to modulate GnRH neuronal activity and gonadotropin production, this effect is variable depending on species, environmental photoperiod and sex.

In rats, mice and sheep, it inhibits GnRH neurons and gonadotropin release (Clarke *et al*., 2008; Anderson *et al*., 2009; Ducret *et al*., 2009; Johnson *et al*., 2007; Pineda *et al*., 2010). In contrast, in the male Syrian hamster, it displays a stimulatory effect on the hypothalamo-pituitary gonadal axis. A chronic administration of RFRP-3 in sexually inactive short day-adapted hamsters fully restore a long day, sexually active phenotype (Ancel *et al*., 2012). In the male Siberian hamster, the effect of RFRP-3 depends on the photoperiodic regimen, being stimulatory in short day- and inhibitory in long day-adapted hamsters (Ubuka *et al*., 2012).

Finally, in female Syrian hamsters, in contrast to males, an acute injection of RFRP-3 at the time of the preovulatory LH surge reduces the amount of LH produced (Henningsen *et al*., 2016). All together, these observations indicate that, although melatonin inhibition of RFRP expression during short day is well conserved among seasonal species, its effect on reproductive activity varies depending on species, environmental photoperiod and sex.

In camels, preliminary results from our laboratory (Ainani, El Bousmaki, Achaâban, Ouassat, Piro, Simonneaux and El Allali, unpublished data) show that neurons expressing RFRP-3 are found in the dorsomedial hypothalamus (Figure 9). Studies are underway to investigate whether this peptide display seasonal variations and whether it can be involved in camel's seasonal breeding.

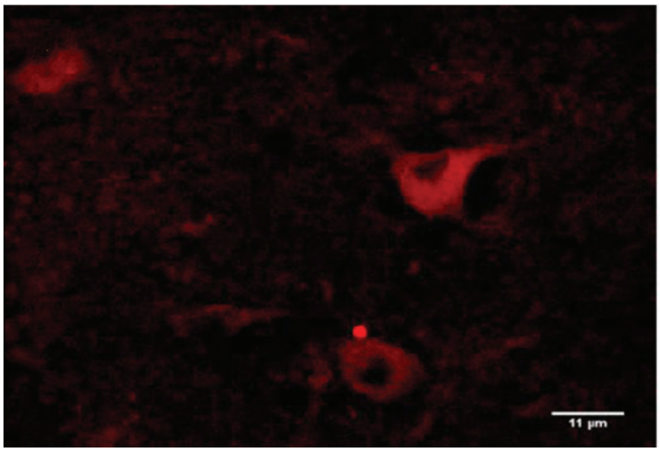

Figure 9: Immunofluorescent labeling of RFRP neurons in the dorsomedial nuclei (DMH) of female camel

CONCLUSION

Food availability for the offspring survival is presumed to be the ultimate factor that determines the breeding season (Lofts, 1975; Gwinner, 1981). Photoperiod and to a less extent ambient temperature and rainfall are considered as proximate factors serving for the prediction of the best timing of good food availability and thus for controlling the breeding season. In camels raised at high latitude, photoperiod and probably ambient temperature are the main factors controlling the breeding season which occurs when photoperiod is short and ambient temperature is low. Mechanisms involved in the control of seasonality by photoperiod are relatively well elucidated. However, there is less evidence how food availability and rainfall can give a direct signal to the brain to modulate the anticipatory response allowing a prediction of breeding seasons.

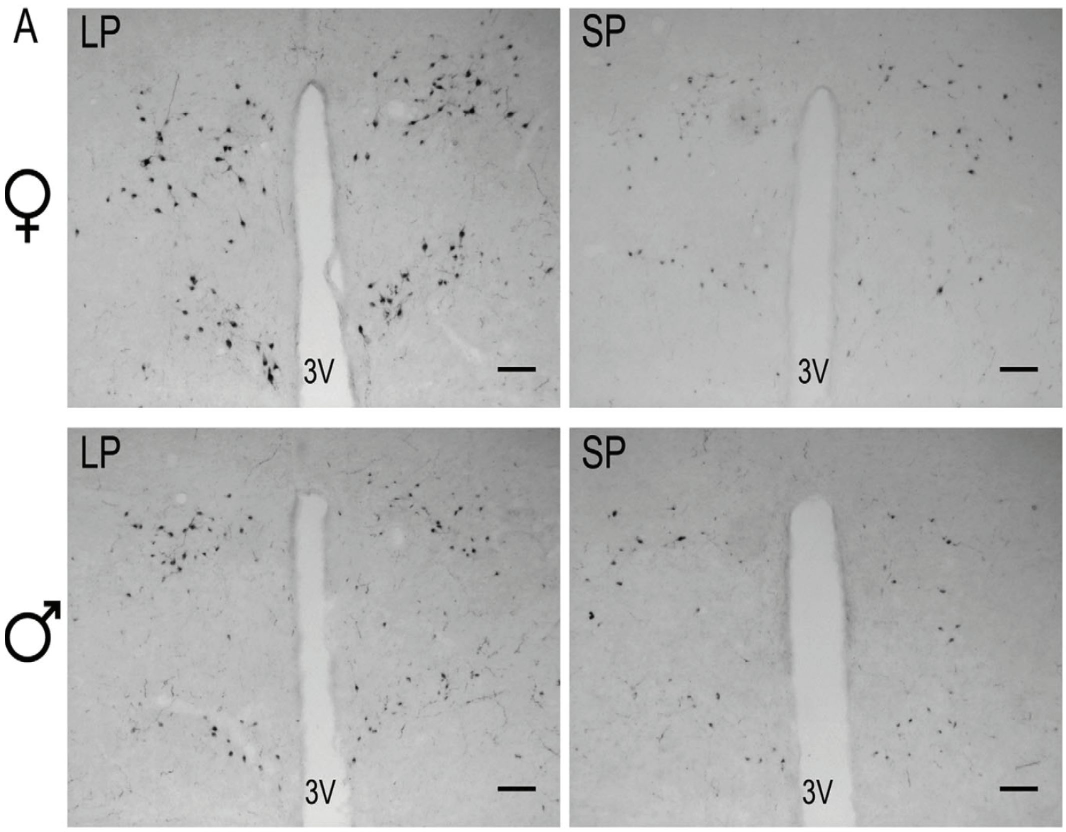

Figure 8: Photoperiodic variations in RFRP expression in the dorsomedial and ventromedial hypothalamus of female and male Syrian hamsters kept in long (LP) or short (SP) photoperiod (from Henningsen et al., 2016)

In harsh environmental conditions, rainfall may become a strong proximate factor, and in these conditions, the camel may display breeding seasons synchronized to rainfall periods.

Photoperiod is a major environmental factor which controls seasonal reproduction via the annual change in nocturnal melatonin secretion. Recent data have pointed to melatonin acting through the regulation of reproductive neuropeptides Kp and RFRP via a TSH secretion from the *pars tuberalis*. Preliminary results in our laboratory show that melatonin injection improves camel reproductive capacity and that Kp and RFRP neurons are present in the camel hypothalamus. Further studies are in progress to investigate how these RF-amide peptides are regulated by proximate environmental factors and whether they are involved in the control of camel reproductive seasonality.

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