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Ghrelin Regulation in Epilepsy

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1. Introduction

Epilepsy is one of the most common neurological problems worldwide affecting approximately 1% of the population (Browne & Holmes, 2000; Chang & Lowenstein, 2003). It is characterized by recurrent unprovoked behavioural seizures (Beck & Elger, 2008).

In recent decades, the relationship between epilepsy and the neuroendocrine system has gained a great deal of interest and many researchers as neurologists, endocrinologists and basic scientists have investigated it. The main issue is whether hormonal changes in relation to epilepsy are due to seizures activity per se or to consequential effects of antiepileptic drugs. To understand the far-reaching effects of epilepsy and antiepileptic medications on hormonal system and vice versa, several studies have been recently performed. Their results are interesting but still controversial and the neuroendocrine regulation of epilepsy is far to be clearly explained.

However, considering that a role of hormones in epilepsy is known and in part well described, this chapter would firstly review the endocrine regulation mediated by sex hormones, prolactin (PRL), growth hormone (GH), thyrotropin-releasing hormone (TRH), adrenocortical axis and neuropeptide Y (NPY). More recently, also other new hormones have been investigated in this field, bringing to light ghrelin. Ghrelin is a 28 amino acid peptide predominantly produced by the stomach (Kojima et al., 1999). It was discovered as the first natural ligand of the orphan growth hormone secretagogues receptor 1a (GHS-R1a), which exerts, through its activation, a strong GH-releasing activity (Arvat et al., 2001; Howard et al., 1996; Kojima et al., 1999; Kojima & Kangawa, 2005; van der Lely et al., 2004). It also influences glucose and insulin metabolism and controls food and energy intake through many neuroendocrine systems (van der Lely et al., 2004). Furthermore, several evidences suggest that ghrelin not only plays a metabolic role but it is also involved in sleep-wake regulation, affective status, learning and memory processes (Steiger et al., 2011; van der Lely et al., 2004). Besides, the recent discovery of ghrelin has also provided an important insight to the neuroendocrine knowledge in epilepsy. In fact, a relationship between ghrelin and epilepsy has been already shown in animal and human models, although the results are sometimes conflicting. Thus, this chapter would secondly describe the intriguing ghrelin role in relation to seizures activity and discuss open questions and future perspectives.

2. The interplay between epilepsy and the endocrine system

Epilepsy and antiepileptic drugs affect hormones and neuroendocrine system. The relationship between epilepsy and the endocrine system is described, in particular for sex

hormones, GH and NPY system. More recently, the role of new hormones in epilepsy like ghrelin and its modulation on GH and NPY has been investigated (Berilgen et al., 2006; Gallagher et al., 1984; Morrell, 2003; Obay et al., 2007; Quigg, 2002; Stroud et al., 2005).

Overall, endocrine disorders related to epilepsy or antiepileptic drugs are a consequence of the influence of epileptogenic lesions, epilepsy or anticonvulsant medications on the endocrine control centers in the brain. Antiepileptic drugs also impact on peripheral endocrine glands, metabolism of hormones and binding proteins, weight and insulin sensitivity (Opaleke & Helmers, 2007).

2.1 Hypothalamus-pituitary-gonads axis

Sex steroids and hypothalamus-pituitary-gonads axis is the most investigated system in epilepsy. Seizures have consequences, in both sexes, on various aspects of the sexual and reproductive functioning and endocrine dysfunctions are reported during childhood, adolescence and adulthood (Opaleke & Helmers, 2007). Postictal hormonal alterations are not relevant after a single seizure; however, endocrine discharges can follow serial uncontrolled seizures, even unrecognized simple partial seizures (Luef, 2010). This is particularly common in temporal lobe epilepsy and it is probably related to the direct connections between this lobe and the reproductive neuroendocrine axis (Opaleke & Helmers, 2007). For example, menstrual disturbances are more frequent in women with epilepsy as compared with those without epilepsy (Svalheim et al., 2003), both in adulthood and in paediatric age (Herzog et al., 1986). In females with epilepsy the most described reproductive endocrine disorder is the polycystic ovary syndrome (Bilo et al., 1988; Herzog & Schachter, 2001). Other common forms of reproductive dysfunctions in women with epilepsy include: hypothalamic amenorrhea with low gonadotropin and estrogen levels and diminished luteinizing hormone (LH) response to the gonadotropin-releasing hormone (GnRH) (Herzog et al., 1986), poly- or oligo-menorrhea, hirsutism, functional hyperprolactinemia with galactorrhea, sub- or infertility and premature menopause (Bauer & Cooper-Mahkorn, 2008). Decreased libido, abnormal semen analysis with reduced sperm count, abnormal sperm morphology and impaired motility and reduced fertility have also been overrepresented in males with epilepsy (Isojarvi et al., 2004). Antiepileptic drugs, as well as seizures, seem to contribute to these sexual and reproductive dysfunctions. These alterations are likely related to a liver enzyme induction, which leads to an increase of the sex hormone-binding globulin and a reduction of the bioavailability of serum-free sex hormone levels in both genders (Opaleke & Helmers, 2007). In contrast, testosterone and androgens are elevated in association with valproate treatments (Herzog et al., 2006; Isojarvi et al., 2004). Clinical data on gonads dysfunctions led to investigate the role of sex hormones on epilepsy mechanisms.

The ovarian sex steroids act in the central nervous system and alter the frequency and the severity of seizures. In human and animal models, estrogen is a potent proconvulsant and progesterone has anticonvulsant properties (Reddy & Rogawski, 2009). Studies also suggested that these hormones might have complex effects depending on many factors like the endocrine state and their relative concentration and metabolism (Scharfman & MacLusky, 2006). In particular, estrogen can stimulate an increase of excitatory neurotransmitters such as glutamate via the N-methyl-D-aspartate (NMDA) receptor and a decrease of inhibitory neurotransmitters such as dopamine, through non-genomic mechanisms (S.S. Smith, 1989) and gamma-aminobutyric acid (GABA) (Ledoux et al., 2009). Estrogen has also an effect on the synaptic areas of neurons leading to an increase of

dendritic spines and cell-to-cell contacts and promoting the hypersynchronization seen in epilepsy. This can contribute to a lowering of the seizure threshold in both hippocampus and amygdala (S.S. Smith, 1989). In addition, it has been observed that estradiol, in parallel with its proconvulsant action, has a mitigating effect to reduce the seizure severity, related to facilitated and increased release of NPY (Ledoux et al., 2009). Progesterone exerts an inhibitory effect via metabolites such as allopregnanolone, which is a GABA-A receptor-modulating neurosteroid. In fact, progesterone increases the seizure threshold and also has antianxiety and sedating effects (Backstrom et al., 1984; Mayewska et al., 1986; Paul & Purdy, 1992).

Androgen metabolites also have some effect on seizure susceptibility, in animals and humans, through testosterone's conversion, with either anticonvulsant or proconvulsant abilities. In particular, aromatization of testosterone to 17beta-estradiol reduces the seizure threshold, whereas 3alpha-androstanediol, which derives by the testosterone's reduction to 5alpha-dihydrotestosterone, has an anticonvulsant effect through a powerful modulation of GABA-A receptor (Reddy, 2004).

2.2 Prolactin

Acute variations in PRL, as well as in gonadotropin levels, following generalized and partial seizures, support the hypothesis of a relationship between temporolimbic epileptiform discharges and reproductive endocrine disorders. In fact, epileptic activity in the temporal structures may propagate to the hypothalamus, altering the hypothalamic regulation of PRL release via a PRL inhibitory factor or dopamine (Parra et al., 1980). In particular, PRL is elevated during phases of simple partial seizures when consciousness is preserved and also rises during the subsequent seizure evolution (Meierkord et al., 1994). Thus, PRL has an immediate postictal elevation, as well as LH, both thought to have clinical values in the diagnosis of epilepsy (Abbott et al., 1980).

2.3 Noradrenaline, vasopressin and oxytocin

It has also been described a fast serum increase of noradrenaline, vasopressin and oxytocin during and after prolonged epileptic temporal seizures. In fact, noradrenaline, vasopressin and oxytocin levels are low during the aura but rapidly increase during the phase in which the epileptic activity evolves from a simple partial to complex partial and finally to the generalisation. In particular, the peak of oxytocin and noradrenaline characterizes the phase of the generalised attack, whereas vasopressin levels peak in the postictal time and remain constantly high for several hours. These findings suggest that the length or the intensity of seizures is important factors influencing the hormonal concentration of noradrenaline, vasopressin and oxytocin, as well as PRL, during limbic seizures (Meierkord et al., 1994).

2.4 Growth hormone and insulin-like growth factor-1

Although most of the data on the physiology of epilepsy are related to sex-hormones, other neuro-hormones have been investigated.

A role of GH in epilepsy has been shown. Epileptic seizures are a side effect of the rhGH replacement therapy (Clayton & Cowell, 2000). In particular, the Kabi International Growth Study (KIGS), a 10-year wide observational study about the GH therapy, recorded seizures as the seventh side effect of the treatment with a prevalence of about 0.5% (Wilton, 1999). The fact that GH has revealed as an important factor in epileptogenesis also emerged from a study

performed by Kato and co-workers, on an amygdala-kindled mice model obtained with electrodes stimulation (Kato et al., 2009). Furthermore, a role of GH for neuronal development, cognitive functions and neuroprotection during hypoxic-ischemic injury, has been reported (Harvey & Hull, 2003; Lyuh et al., 2007; Mahmoud & Grover, 2006; Nyberg, 2000; Ramsey et al., 2004; Scheepens et al., 2001). However, KIGS was the first study that evidenced that GH enhances epileptic seizures progression. This is a consequence of the increase of endogenous GH expression and the signalling of the hormone itself along neuronal circuits, which propagate kindling-stimuli in hippocampus and cortex, but not in the pituitary (Kato et al., 2009). Moreover, the injection of GH into the hippocampus strongly promotes the progression of the kindling, whereas the direct administration of an inhibitor, such as octreotide, elicits a delay in the behavioural development during epileptogenesis (Kato et al., 2009). In particular, GH is involved in a biochemical pathway that seems to affect excitatory postsynaptic potentials on hippocampal synaptic transmission via the modulation of α -amino-3-hydroxy-5-methylisoxazole-4-propionate and NMDA-receptor (Mahmoud & Grover, 2006).

Pathophysiological events, such as ischemia and status epilepticus, increase cell proliferation through insulin-like growth factor-1 (IGF-1). Its expression is up-regulated in the reactive microglia near to the subgranular zone of the dentate gyrus at 2-days after a status epilepticus. It firstly promotes the release of glutamate; secondly, mitogen-activated protein kinase (MAPK) cascade and finally it increases the rate of proliferation of cell's progenitors (Aberg et al., 2000, 2003; Choi et al., 2008; Kurihara et al., 2000). Probably the involvement of GH signalling not regards the GH-receptor (GHR); in fact, an increase of neuronal proliferation in the subgranular zone of the dentate gyrus has been shown in GHR knockout mice (Ransome & Turnley, 2008). The neuronal plasticity related to GH suggests the possibility of therapeutic interventions against neurodegenerative disorders in the older age; however, recent data also indicate that these newly generated neurons are integrated into epileptogenic networks in animal models (Siebzehntrubl & Blumcke, 2008), suggesting that neurogenesis contributes to promote susceptibility to seizures.

2.5 Thyrotropin-releasing hormone

Over the past years, the neuromodulatory role of TRH has been investigated. TRH participates to the regulation of hypothalamic-pituitary-thyroid axis but it is also a neuropeptide and it exerts its functions in the brain, particularly in the hippocampus and in other neural tissues (Gary et al., 2003; Kubek et al., 1977; Nillni & Sevarino, 1999). There are several findings that support an anticonvulsant effect of TRH in the regulation of seizure susceptibility (Jaworska-Feil et al., 1999, 2001; Knoblauch & Kubek, 1997a, 1997b; Kubek et al., 1989; Kubek & Garg, 2002; Wan et al., 1998). Its mechanism of action is poorly understood; however, it seems to be implicated in a protection against neuronal overexcitability. In fact, some authors reported that TRH could inhibit the effects of the glutamate-induced toxicity, in a dose-dependent manner, in cultured fetal rat hippocampal neurons (Pizzi et al., 1999; Veronesi et al., 2007). Furthermore, a paradoxical secretory peak of GH to TRH is more frequent during a status epilepticus. A GH release after an intravenous TRH administration in patients with a status epilepticus suggests an abnormal regulation of GH as a consequence of the long-standing epileptic activity (Lindborn et al., 1999).

2.6 Hypothalamic-pituitary-adrenocortical system

A marked hormonal dysregulation of the hypothalamic-pituitary-adrenocortical system, independent of administered medications, has been found in patients with epilepsy. In fact,

in these patients increased circulating levels of cortisol and adrenocorticotrophic hormone (ACTH) are measured, relating to a deficient inhibitory feedback system after the suppression by dexamethasone (Zobel et al., 2004). These data have been confirmed by Galimberti and co-workers who reported decreased levels of dehydroepiandrosterone sulphate (DHEAS), in women with frequent seizures; this is not merely due to enzyme-inducing antiepileptic drugs (Galimberti et al., 2005). These findings recognize the involvement of the hippocampus and/or amygdala, which are target regions for the control of hypothalamic-pituitary-adrenocortical system and which contribute to the generation and propagation of seizures (Aliashkevich et al., 2003; Heimer, 2003). Furthermore, repetitive seizures themselves induce a hypothalamic-pituitary-adrenocortical dysfunction, in relation to chronic stressful events, which is independent of the localization of the epileptogenic focus (Checkley, 1996; De Kloet, 1995; Holsboer, 2001; Kudielka et al., 1999).

Increased basal cortisol levels, measured in salivary samples, have been recently described in patients with psychogenic nonepileptic seizures as independent of the acute occurrence of seizures; in addition, a basal hypercortisolism is present in patients with a trauma history, underling an involvement of psychological stress factors (Bakvis et al., 2010). However, further studies about the time of the onset of a blunted inhibitory control of hypothalamic-pituitary-adrenocortical system, are important to understand if this discharge is only a secondary effect of seizures or whether it also determines a susceptibility to epilepsy (Zobel et al., 2004). At this regard, it is known that the hypercortisolism observed in several neuropsychiatric disorders is partially due to reduced neuronal outgrowth and plasticity with a lower hippocampus volume and cognitive deficits (McEwen et al., 1992; Sapolsky, 2000; Sapolsky et al., 1986; Sheline et al., 1996).

In addition, opposite effects on neuron survival have been attributed to cortisol and DHEAS. Cortisol exerts a neurotoxic effect, affecting cerebral glucose metabolism and enhancing calcium influx in hippocampal neurons (McEwen & Magarinos, 1997; Sapolsky et al., 1986). By contrast, DHEAS has a neuroprotective activity, inhibiting GABA-induced chloride transmembrane transport and antagonizing NMDA negative effects on neurons in relation to an increased calcium influx (Baulieu & Robel, 1996; Beyenburg et al., 2001; Kimonides et al., 1998; Mayewska, 1995; Watzka et al., 2000). Thus, these mechanisms are involved in neuron excitability and seizures. However, an intracerebroventricular injection of DHEAS in animals induces seizures (Czlonkowska et al., 2000), so the actual effects in vivo remain further unclear.

Instead it is widely demonstrated that ACTH has a neurotrophic effect, promoting recovery from damages in both the peripheral and central nervous system (Darlington et al., 1996; Kokubo et al., 2002), the ACTH mechanism in epilepsy is not fully understood. It has an anticonvulsant action by itself, enhancing GABA-receptors via deoxycorticosterone synthesis (Rogawski & Reddy, 2002) and downregulating corticotropin releasing hormone (CRH) expression, which is a proconvulsant agent in the immature brain (Baram & Hatalski, 1998). Actually, ACTH is well accepted as an effective therapy for infantile spasms, one of the intractable types of epilepsy that occurs in infancy and early childhood (Mackay et al., 2004).

2.7 Neuropeptide Y

NPY, which is widely distributed throughout the central nervous system, including the hippocampus, is an endogenous anticonvulsant; it is known to prevent seizures in rats (De Quidt & Emson, 1986) by increasing the seizure threshold (Dubè et al., 1999). Although the

relationship between NPY and epilepsy has not been completely investigated in humans, the extensively studies in animal models suggest a critical role of NPY in regulating the excessive synaptic excitation associated with an epileptic seizure (Colmers et al., 1987; Haas et al., 1987).

Plasma concentrations of NPY were lower in human patients with atypical febrile convulsions than those with typical ones, suggesting that low NPY levels could increase the risk of long-lasting seizures or recurrent febrile convulsions and make patients more susceptible to epilepsy, independently by gender, both in adults (Lin et al., 2007) and children (Lin et al., 2010).

Recently, ghrelin has been isolated from the stomach and has been recognized as the first endogenous ligand of the GSH-R1a (Korbonits et al., 2004; Weikel et al., 2003). Ghrelin is able to stimulate GH secretion but it also has pleiotropic activities, it influences cardiac and gastrointestinal functions, carbohydrate metabolism, adipose and reproductive tissues, sleep, feeding and energy intake. The control of food and energy intake is mediated by effects on NPY (Korbonits et al., 2004; Tolle et al., 2002; van der Lely et al., 2004; Weikel et al., 2003). Given the relationship between epilepsy and NPY, some authors focused their attention on this new hormone. Actually, the physiologic role of ghrelin in this complex network has not been clearly established and the association between epilepsy and ghrelin is still controversial. However, the recent discovery of ghrelin has provided an important insight to this field and we will focus on these new aspects.

3. Ghrelin regulation and functions

Ghrelin is a 28 amino acid peptide predominantly produced by the stomach, particularly in the A/X-like cells that account for 20-25% of all the endocrine cells in the oxyntic mucosa (Kojima et al., 1999). It was discovered as the first natural ligand of the orphan GHS-R1a, which exerts, through its activation, a strong GH-releasing activity (Howard et al., 1996; Kojima et al., 1999; Kojima & Kangawa, 2005; van der Lely et al., 2004); for its binding to and the activation of the GHS-R1a, the acylation of ghrelin with a medium fatty n-octanoic acid on the Ser3 residue seems to be essential. This mechanism is largely unknown (Kojima et al., 1999; van der Lely et al., 2004). Despite this background, unacylated ghrelin (UAG), which is devoid of the n-octanoil group at Ser3, is the most abundant circulating form and the ratio between UAG and acylated ghrelin (AG) is either 3:1 or 4:1 (Gauna et al., 2004; Kojima et al., 1999; Kojima & Kangawa, 2005; Korbonits et al., 2004). The regulation of AG and UAG circulating levels has not yet been clearly defined. It is thought that UAG could be produced directly from the ghrelin gene, via a different pathway to the acylated form or alternatively it could be derived by the deacylation of ghrelin (Liu et al., 2008; Soares & Leite-Moreira, 2008). Very recently ghrelin O-acyltransferase (GOAT), an enzyme catalyzing the addition of the octanoyl-group, has been identified (Gualillo et al., 2008). It is not known at present whether the GOAT levels regulate changes in ghrelin acylation or, on the contrary, if GOAT itself depends on different metabolic conditions. Originally AG was supposed to be the only biologically active hormonal form (Broglia et al., 2008; Kojima & Kangawa, 2005; van der Lely et al., 2004); however, there is increasing evidence that demonstrates that UAG is also a biologically active molecule, although it is unable to cross the blood brain barrier and to exert a direct action on hypothalamus-pituitary (Broglia et al., 2004a; Gauna et al., 2005; Gil-Campos et al., 2006; Wiedmer et al., 2007). This is consistent with the hypothesis

of the existence of some GHS-R subtypes that are activated independently by the ghrelin's acylation (Kojima et al., 1999; Kojima & Kangawa, 2005; van der Lely et al., 2004).

Ghrelin is predominantly expressed and secreted by the stomach (Kojima et al., 1999), unless during fetal life, when the major site of its production is the endocrine pancreas (Chanoine & Wong, 2004). Ghrelin expression has also been demonstrated in several other tissues, such as adrenal gland, breast, testis, thyroid, myocardium, muscle and colon (Gnanapavan et al., 2002; van der Lely et al., 2004). The ghrelin target, GHS-R1a, is remarkably expressed in the hypothalamus-pituitary unit and, in parallel with ghrelin, it has also been demonstrated in several peripheral endocrine and non-endocrine tissues (van der Lely et al., 2004).

This widespread distribution could mediate the multiple actions of ghrelin. In addition to the GH releasing effect, ghrelin emerged as one of the most powerful orexigenic and adipogenic agents known so far (Arvat et al., 2001; Cummings et al., 2001; Korbonits et al., 2004; Leite-Moreira & Soares, 2007; van der Lely et al., 2004). The NPY and Agouti-related protein (AgRP) co-mediate ghrelin's effects on energy balance in the hypothalamus, in the arcuate nucleus (Chen et al., 2004; Gil-Campos et al., 2006; van der Lely et al., 2004). Furthermore, ghrelin regulation of energy balance also seems to be influenced by efferent and afferent fibers of the vagal nerve and other neuroendocrine factors as orexins, GABA, cocaine-amphetamine regulated transcript (CART) and CRH (Asakawa et al., 2001b; Gil-Campos et al., 2006; Leite-Moreira & Soares, 2007). The adipogenic action of ghrelin consists of an increase in fat mass induced by a reduction of cellular fat oxidation and a promotion of adipogenesis. This action can reflect both its orexigenic action and central modulator effect on energy expenditure (Gil-Campos et al., 2006; Leite-Moreira & Soares, 2007; Thompson et al., 2004; van der Lely et al., 2004; Wiedmer et al., 2007). Furthermore, several studies clearly indicated the existence of direct effects on the adipose tissue (Thompson et al., 2004; van der Lely et al., 2004; W. Zhang et al., 2004); at least in part, this is due to a decrease in fat utilization and an increase in fat tissue content (Leite-Moreira & Soares, 2007; Tschöp et al., 2000; van der Lely et al., 2004). Additionally, considering adipose tissue, UAG and AG are active in modulating lipolysis, such both UAG and AG seem to affect in the same way adipocyte function and to determine a lipogenic pattern (Muccioli et al., 2004). In contrast, UAG and AG play opposite effects on food intake, gastric emptying, pancreatic beta-cell secretion and glucose metabolism (Prodam et al., 2008). In fact, if AG may contribute to the worsening of insulin sensitivity, suggesting a diabetogenic function, UAG could exert its metabolic actions counterbalancing those of AG, at least in part at the pancreatic level (Ariyasu et al., 2005; Broglio et al., 2004a; Gauna et al., 2005).

Considering ghrelin regulation, in humans it has a pulsatory secretion, with higher secretion at night-time as it undergoes circadian variations with a decrease following food ingestion that suggests a metabolic control (Cummings, 2006; Cummings et al., 2001; van der Lely et al., 2004). The depth and duration of ghrelin decrease after a meal is related to the total amount of calories ingested and to the type of the macronutrients, such as carbohydrates and proteins in spite of less effective suppression led by lipids (Prodam et al., 2006; Leite-Moreira & Soares, 2007; van der Lely et al., 2004). In particular, meals inhibited secretion of both AG and UAG. Acylation may be regulated independently of secretion by nutrient availability in the gut or by esterases that cleave the acyl-group (Liu et al., 2008). Furthermore, ghrelin secretion is also under cholinergic control (Broglio et al., 2004b) and it is regulated by other factors that are involved in energy balance and metabolism, such as glucan-like peptide 1 (GLP-1), peptide YY (PYY), oxyntomodulin, urocortin, thyroid hormones, glucocorticoids, insulin and gonadal steroids (Baldelli et al., 2006; Gil-Campos et

al., 2006; Korbonits et al., 2004; Leite-Moreira & Soares, 2007; van der Lely et al., 2004; Wiedmer et al., 2007).

As mentioned below, the circulating levels of ghrelin are firstly modulated by energy balance and nutrition status; in particular, ghrelin levels are negatively associated with body mass index, with ghrelin secretion increased in anorexia and cachexia and reduced in obesity, with normalization achieved through the recovery to an ideal body weight (Tschöp et al., 2001; Leite-Moreira & Soares, 2007; van der Lely et al., 2004). Furthermore, circadian ghrelin secretion is abnormal in obesity, as there is an absent or an altered ghrelin elevation during fasting (Perreault et al., 2004) and an abolished or a blunted increase during the night or sleep deprivation (Vazquez et al., 2006; Yildiz et al., 2004) and blunted suppression following a meal (English et al., 2002). The most likely explanations could be that low ghrelin levels in essential obesity are related to increased insulin resistance and consequent hyperinsulinemia with weight excess. However, it may also reflect a compensatory mechanism by communicating to central regulatory centres that energy stores are sufficiently filled (Cummings, 2006; van der Lely et al., 2004). Therefore, conditions characterized by insulin resistance, such as polycystic ovarian syndrome (Pagotto et al., 2002), type 2 diabetes and metabolic syndrome (Erdmann et al., 2005; Langenberg et al., 2005), have low ghrelin levels too.

The only clinical exception to this picture is the Prader-Willi syndrome, a complex multi-systemic genetic disease caused by the lack of expression of paternally inherited genes imprinted and located in the chromosome 15q11-q13 region (Goldstone et al., 2008; Nicholls et al., 1989). Although genotype-phenotype correlations have been widely described, it can be summarized that Prader-Willi syndrome is characterized by typical features including neonatal hypotonia, uncontrolled and precocious hyperphagia, severe obesity with typical fat distribution, short stature, hypogonadism and other somatic, endocrine and psychological problems (Goldstone et al., 2004; Goldstone et al., 2008). These many phenotypes may depend on hypothalamus-pituitary and brain signalling derangements (Bellone et al., 2011). Interestingly, it has to be underlined that the Prader-Willi syndrome neuroendocrine and metabolic patterns are partly different to what occurs in simple obesity; in fact, unlike essential obesity, patients with Prader-Willi syndrome show elevated ghrelin levels (DelParigi et al., 2002; Goldstone, 2004; Paik et al., 2004, 2006). Since the exact pathogenetic mechanism leading to the Prader-Willi syndrome phenotype are at present unknown, ghrelin hypersecretion has been obviously hypothesized to participate in the development of at least some symptoms such as hyperphagia and weight excess (DelParigi et al., 2002; Paik et al., 2004). However, growing data suggested that hyperghrelinemia in Prader-Willi syndrome could be more likely a compensatory mechanism to other biochemical and hormonal alterations, in particular neonatal hypoglycaemia and relative hypoinsulinemia, to restore normal glucose levels or glucose sensing (Bellone et al., 2011).

Several studies also suggested that ghrelin is one of the mediators of behaviours linked to food intake and body weight and of those associated with psychological stress, mood and anxiety (Chuang & Zigman, 2010). In fact, ghrelin rises in response to stressful events both in mice (Lutter et al., 2008b) and humans (Rouach et al., 2007). It has been proposed that higher ghrelin levels help in promoting antidepressant-like behavioural adaptations (Lutter et al., 2008b); for example it increases neuronal activity in brain reward centers in humans when images of appealing food are shown (Malik et al., 2008). Studies about the relationship between ghrelin and mood showed that a GSH-R1a polymorphism is related to major depressive disorders (Nakashima et al., 2008). Mechanisms by which ghrelin is able to

modulate mood are not completely explained; however, ghrelin's action on mood seems to be due to: 1) direct and indirect feedbacks on the orexin system; 2) interactions with neuronal circuits involved in motivation and rewards; 3) effects on reward-associated memories and the ability to experience pleasure; 4) modulation of hippocampal neurogenesis and brain inflammation (Lutter et al., 2008a, 2008b; Chuang & Zigman, 2010). By contrast, other studies suggested that rising ghrelin would contribute to the development of stress-induced depression and anxiety (Asakawa et al., 2001a; Carlini et al., 2002, 2004; Carvajal et al., 2009).

Furthermore, increasing evidence indicates that ghrelin not only plays a role in anxiety and stress, but it is also involved in promoting learning behaviour and memory processes and in sleep-wake regulation (Steiger et al., 2011). In particular, a sleep-promoting potential of ghrelin has been supported (Steiger et al., 2011). Szentirmai and co-workers reported that ghrelin knock out rodents sleep less than wild type ones (Szentirmai et al., 2007). In accordance with a sleep-promoting effect of ghrelin, knockout mice for ghrelin had impaired physiologic sleep regulation and thermoregulatory responses too. Thus, in response to fasting at 17 °C, these knockout mice presented hypothermic bousts associated with a reduced sleep (Szentirmai et al., 2009).

Furthermore, also previous studies in humans suggested a sleep-promoting effect of ghrelin, with the evidence of its peaks around the sleep onset (Dzaja et al., 2004). This finding was not supported by Schussler and co-workers, who described in subjects with higher nocturnal ghrelin levels, a lower time spent in the stage 1 of sleep that means shallow sleep suggesting a promotion of sleep by ghrelin (Schussler et al., 2005). Schussler and co-workers also showed increased ghrelin levels during the recovery night after a sleep deprivation period, supporting the idea that an endogenous substance diverse from ghrelin accumulates during the sleep deprivation and it is a candidate to be a promoting factor of sleep. Higher ghrelin levels in sleep deprivation, in association with other hormonal derangements, could be a root cause of the dysregulation of hunger, appetite and metabolism linked to sleep loss or sleep alterations (Van Cauter et al., 2008; Van Cauter & Knutson, 2008). In addition, ghrelin levels are lower in the insomnia patients across the night (Motivala et al., 2009).

In conclusion, the action of ghrelin includes much more than the energetic homeostasis and affects a more complex pathway not yet known.

4. Ghrelin and epilepsy: In vitro and in animal studies

A relationship between ghrelin and epilepsy has been demonstrated in animal and human models, although the results are still controversial (Dag et al., 2010).

Some studies suggested an anticonvulsant effect of ghrelin. In fact, the intraperitoneally injection of ghrelin was able to delay or prevent the development of pentylenetetrazole (PTZ)-induced seizures in rats, supporting the hypothesis of an inhibitory effect on the emergence and the severity of seizures. However, dose-dependent ghrelin administrations reduced but not completely abolished the intensity of PTZ-induced seizures in rats (Obay et al., 2007). The mechanism related to the antiepileptic and the preventive role of ghrelin has been explained, firstly, through the enhancing of NPY and GABA activity in the brain (Cowley et al., 2003). In the arcuate nucleus of the hypothalamus, ghrelin fibers form axo-somatic and axo-dendritic contacts with both proopiomelanocortin (POMC) and NPY/AgRP neurons (Cowley et al., 2003). The direct link between the brain-derived ghrelin and the central melanocortin system has been supported by electrophysiological

demonstration: ghrelin increases the firing of arcuate NPY/AgRP neurons, which increase GABA-ergic inhibitory post-synaptic currents into POMC neurons (Cowley et al., 2001). Secondly, ghrelin can be considered as an anticonvulsant agent by stimulating vagal nerve (Macdonalds, 1997). In fact vagal nerve stimulations are associated with a reduction of the seizure frequency more than 50% in about 30% of patients who are refractory to epilepsy treatments (Ben-Menachem et al., 1999; Handforth et al., 1998; Morris & Mueller, 1999).

The oxidative stress in the central nervous system in relation to discharges in the epileptic rat brain has been reported in several rodent models of epilepsy (Bruce & Baudry, 1995; Erakovic et al., 2003; Singh & Pathak, 1990; Veerendra Kumar & Gupta, 2003). At this regard, there is emerging evidence that oxidative stress and mitochondrial dysfunctions result as a consequence and a cause of seizures (Patel, 2002). In fact, free oxygen radicals contribute to the genesis of seizure activity by direct inactivation of glutamine synthase and glutamate decarboxylase, such promoting an abnormal build-up of excitatory (glutamate) and inhibitory GABA neurotransmitters (Atmaca & Fry, 1996; Oliver et al., 1990; Sudha et al., 2001). In addition, seizure itself is associated with an important production of reactive oxygen species (Mueller et al., 2001). It has also been suggested that oxidative stress could occur during anticonvulsant therapies, likely related to detrimental effects on the antioxidant defence system, in particular with a significant decrease in plasma glutathione levels (Ono et al., 2000; Uma Devi et al., 2006). In the light of this knowledge, Obay and co-workers supported the hypothesis that ghrelin might be an antioxidant and an anti-inflammatory agent therefore it exerted protective effects in PTZ-induced epileptic rats (ISeri et al., 2005; Obay et al., 2007). In particular, in PTZ-induced epileptic rats there was an increase in the oxidative stress, with higher lipid peroxidation in erythrocytes, liver and brain tissues, whereas enzymes which have antioxidant activities (superoxide dismutase - SOD, catalase -CAT) and glutathione levels were significantly reduced; all these alterations are prevented by an intraperitoneally ghrelin pretreatment (Obay et al., 2008).

Recently, neuroprotective effects of ghrelin on pilocarpine-induced seizures in rodent models have also been investigated (Xu et al., 2009). Pilocarpine-induced seizures cause a neuronal loss in the hippocampus and ghrelin seems to be able to protect hippocampal neurons against this cell death. According with previous studies reporting that ghrelin activates the phosphoinositide-3-kinase (PI3K)/Akt pathway in hypothalamic neurons (Chung et al., 2007), a mechanism which plays a central role in intracellular processes such as survival and proliferation (Cuevas et al., 2001; Franke et al., 1997; Henshall et al., 2002), it has been demonstrated that ghrelin strongly up-regulates the seizure-induced decrease in phospho-PI3K and phospho-Akt in the hippocampus, rescuing neuronal cells from death induced by seizures (Xu et al., 2009). Furthermore, anti-apoptotic actions of ghrelin are also confirmed by data of the effects on mitochondrial pathways (Miao et al., 2007; Xu et al., 2009; Y. Zhang et al., 2007). In particular, pilocarpine-induced seizures result in increased Bax and decreased Bcl-2 with consequentially a decreased ratio of Bcl-2 to Bax and an activation of caspase-3 in the hippocampus at 24 h after pilocarpine treatments. The ghrelin pretreatment prevents the decreased ratio of Bcl-2 to Bax induced by seizures and inhibits caspase-3 activation, such protecting by the hippocampal neuronal damage (Xu et al., 2009). However, it is unclear whether the neuroprotective effect of ghrelin is due to the activation of the GHS-R1a or of an unknown receptor in hippocampus (Xu et al., 2009).

Ghrelin also prevents the kainic acid-induced activation of microglia and astrocytes and the expression of pro-inflammatory mediators as well as tumor necrosis factor alpha, interleukin-1beta and cyclooxygenase-2 with the inhibition of the matrix

metalloproteinase-3 expression which is related to the damaged of hippocampal neurons (Lee et al., 2010).

A recent study showed not only the effect of ghrelin in the penicillin-induced seizures, confirming its antiepileptic action but also the role of nitric oxide (NO) on the effect of ghrelin (Aslan et al., 2009). In fact, several effects exerted by ghrelin involve NO pathway by stimulating NO synthesis (Korbonits et al., 2004) whose role has also been investigated in neurological diseases such as epilepsy (Bosnak et al., 2007; Gaskin et al., 2003; Korbonits et al., 2004; S. E. Smith et al., 1996). Indeed, the antiepileptiform activity of ghrelin was reversed by a non specific nitric oxide synthase inhibitor (L-NAME), but not by a selective neuronal nitric oxide synthase inhibitor (7-NI). This evidence indicated that ghrelin could need an activation by the endothelial nitric oxide synthase (NOS)/NO route in the brain and suggested NO as an intermediate effector in the functional balance between excitatory and inhibitory neurotransmitter systems related to ghrelin (Aslan et al., 2009).

Some studies have been conducted also in animals focusing on regulation of ghrelin secretion in epilepsy or after seizures. Blood AG levels decreased after the PTZ-induced seizures in rats with a similar but not significant trend for UAG and total blood ghrelin levels (Ataie et al., 2011). These decreases could be modulated by hormones which inhibit the production, acylation or secretion of ghrelin, such as somatostatin and leptin (Ataie et al., 2011). Somatostatin, preferentially released from neurons under conditions of high neuronal activation, for example during seizures (Vezzani & Hoyer, 1999), is able to blunt ghrelin secretion in animals (Shimada et al., 2003; Silva et al., 2005; van der Lely et al., 2004) and humans (Broglia et al., 2002, 2007; van der Lely et al., 2004). In addition, it has been reported that somatostatin decreases the GOAT expression (Gahete et al., 2010; Gualillo et al., 2008). Then, a rapid rebound of UAG levels respect to those of AG, related to this mechanism, may explain the partial reduction of UAG and total ghrelin levels after the PTZ-induced seizure (Ataie et al., 2011). Moreover, some studies described high serum leptin levels in rats after seizures (Bhatt et al., 2005; Hum et al., 2009), which could directly inhibit ghrelin secretion as shown in other animal models (Kamegai et al., 2004). Another possible explanation about lower AG blood levels, is an increased uptake of AG by brain structures influenced by pathophysiological events to modulate epileptic discharges (Ataie et al., 2011; Banks et al., 2002). Furthermore, other mechanisms such as proteolysis of AG and degradation into non-UAG metabolites could occur during seizures (De Vriese et al., 2004; Ni et al., 2010); both of them may contribute to the reduction of blood ghrelin levels immediately after the epileptic seizures in animals (Ataie et al., 2011).

In conclusion, ghrelin can be considered as a neuroprotective agent, exerting antiepileptic, antioxidant or anti-inflammatory properties at least *in vitro* and in animal models. However, the anticonvulsant ghrelin mechanism has not been yet completely understood, in particular the regulation of its secretion after seizures.

5. Ghrelin and epilepsy in humans

The attention of researchers has been directed to investigate the role of ghrelin in epilepsy firstly in animals and secondly in humans.

In one of the first studies in epileptic subjects, serum total ghrelin levels were higher in patients than in controls, in contrast to data in animal models (Ataie et al., 2011; Berilgen et al., 2006; Obay et al., 2007). In addition to its effect on weight regulation and glucose and lipid metabolism, ghrelin has also been shown to act on the release of GH, ACTH and PRL

(Arvat et al., 2001; Korbonits et al., 2004, van der Lely et al., 2004). Besides, it is proposed that higher ghrelin levels could facilitate the emergence of seizures by affecting GH and PRL secretion and by disrupting hormonal homeostasis (Berilgen et al., 2006). Furthermore, ghrelin has been described as a factor in sleep regulation able to promote the slow-wave sleep and prolong non rapid eye movements (NREM) sleep during the night (Weikel et al., 2003; Van Cauter et al., 2008; Van Cauter & Knutson, 2008). Therefore, higher serum levels of ghrelin in epileptic patients might be interpreted as a contributing factor to the genesis of seizures, considering that NREM is the stage in which seizures tend to occur (Berilgen et al., 2006). Finally, authors suggested that higher serum ghrelin levels indicate a predisposition toward seizure activity (Berilgen et al., 2006).

Greco and co-workers reported that circulating ghrelin levels in epileptic patients treated with valproic acid were decreased and they were significantly lower than those of patients who did not gain weight; however, this study did not rule out whether lower ghrelin levels were due to weight accrual or puberty (Greco et al., 2005). Taking into account antiepileptic treatments and weight, another study demonstrated that circulating ghrelin levels were decreased in young epileptic prepubertal normal weight children treated with carbamazepine and valproic acid during the first years of therapy, prior to and independent of a consistent drug-induced weight gain (Ness-Abramof & Apovian, 2005; Prodam et al., 2009). The choice to enrol only young prepubertal children was related to avoid the well-known modulation of ghrelin secretion by pubertal stage and age (van der Lely et al., 2004). In fact, the study of Berilgen and co-workers showed controversial results considering all epileptic subjects from childhood to adulthood and their data may be explained by a multitude of factors including the recruitment of an older population with a longer history of antiepileptic therapy and the different auxological stages (Berilgen et al., 2006; Prodam et al., 2009). Moreover, although ghrelin levels were reduced in the entire sample, patients under treatment with valproic acid showed higher ghrelin levels than those under carbamazepine, suggesting an involvement of valproic acid in a positive feedback regulation of ghrelin levels (Berilgen et al., 2006; Prodam et al., 2009).

This study also demonstrated a positive correlation between lower ghrelin levels and the negative variation of the height standard deviation score with respect to the baseline of therapy with carbamazepine in patients who were drug-naïve, hypothesizing that lower ghrelin levels could worsen the variation height standard deviation score (Prodam et al., 2009). The fact that physical growth seems to be affected in paediatrics patients with epilepsy also emerges in a study recently performed by El-Khayat and co-workers (El-Khayat et al., 2010). Height was lower in patients with epilepsy and they presented significantly lower levels of GH and IGF-1 after provocation with L-dopa compared to the control group (El-Khayat et al., 2010). Actually, the question arises whether the decreased GH release might be related to the direct negative effect on the hypothalamus-pituitary axis due to seizure activity per se or to antiepileptic drugs. Likely, these findings can be explained as a consequence of a hormonal imbalance related to both events (El-Khayat et al., 2010). A possible mechanism is the reduction of GABA concentration and of GABA receptor binding that are both demonstrated in cortical epileptic specimens (Bakay & Harris, 1981). In fact, GABA agonists are able to stimulate GH release (Tamminga et al., 1978). Instead, the possible role of enzyme inducing antiepileptic drugs on promoting GH metabolism wasn't evident in this study (El-Khayat et al., 2010). The reduction of height associated with lower GH and IGF-1 levels in children with epilepsy might be a consequence of lower ghrelin levels or of a blunted ghrelin action on pituitary (van der Lely et al., 2004; Zizzari et al., 2005).

The most recent study was designed to indicate candidate biomarkers for the diagnosis of epilepsy and for the monitoring of the response to anticonvulsant drugs, dosing ghrelin and other hormones with simpler and non-invasive tests (Aydin et al., 2009). Besides, Aydin and co-workers recorded lower ghrelin levels in serum and saliva, in association with higher serum and saliva levels of nesfatin-1 (Aydin et al., 2009). Nesfatin-1 is a satiety hormone recently discovered, expressed in hypothalamic nuclei (Kohno et al., 2008; Oh-I et al., 2006; Pan et al., 2007; T. O. Price et al., 2007) in epileptic patients. These results were more evident before the starting of antiepileptic treatments and they weren't explained yet. However, it has been hypothesized that an excessive release of nesfatin-1 might cause an excitotoxicity, stimulating hyperpolarization and depolarization in paraventricular and arcuate nuclei (T. O. Price et al., 2007; C. J. Price et al., 2008). However, the question whether higher nesfatin-1 and lower ghrelin levels are a root cause of epilepsy or epilepsy modulates them has not been answered yet (Aydin et al., 2009).

Similar results were reported by Dag and co-workers who showed that serum chromogranin A and obestatin were up-regulated whereas serum total ghrelin were down-regulated in epileptic patients previously or currently treated with drugs, with salivary hormone concentrations resembling those in serum (Dag et al., 2010). Chromogranin A is an acidic glycoprotein located in the secretory vesicles of neurons and endocrine cells (Hendy et al., 1995), actually known as a stress indicator (Zheng & Moritani, 2008). Instead, obestatin, a bioactive peptide hormone, derives from the pre-proghrelin sequence and it is also involved in a wide range of physiological functions. It was considered as a ghrelin antagonist but more recent findings not confirm this role (Tang et al., 2008; J. V. Zhang et al., 2005). The exact mechanism of the relationship between ghrelin and obestatin has not been completely explained, in particular in epileptic patients. An important unresolved question is why ghrelin and obestatin levels do not show parallel decrements or increments since they are products of the same gene (Dag et al., 2010). However, also these data supported that ghrelin levels are reduced in epilepsy and that saliva might be a good alternative for measuring these hormones in the diagnosis and follow-up of epilepsy (Dag et al., 2010).

In addition, some authors found reduced high density lipoprotein (HDL)-cholesterol serum levels in epileptic patients (Aydin et al., 2009; Dag et al., 2010); so a parallel decrease both in ghrelin and HDL-cholesterol concentrations may be expected, because ghrelin is a HDL-cholesterol-associated hormone (Beaumont et al., 2003).

Therefore, more studies are needed to clarify the complex pathway system involved in epilepsy and, in particular, the exact role of ghrelin and obestatin.

6. Conclusions

Epilepsy and antiepileptic drugs affect the neuroendocrine system and seizure threshold may be altered in relation to these hormonal modifications. Actually, the knowledge about neuroendocrine regulation in epilepsy is far to be complete and it is yet elusive. However, current findings suggest a complex network in which hormones play a crucial role as both as a cause and as a consequence of the epileptic activity. Thus, further studies are needed, in particular to fully define the role of new identified hormones, as ghrelin. Since the current knowledge, the effects of ghrelin include much more than those on pituitary and energy homeostasis. Increasing evidence indicates that ghrelin plays a role in anxiety and stress, in promoting learning behaviour, memory processes and sleep-wake regulation. Considering ghrelin pleiotropic functions, it has a relationship with epilepsy and seizures. Actually, the

results of the studies in vitro and in vivo are still controversial. However, it could be assured that ghrelin has anticonvulsant properties. In fact, focusing on regulation of ghrelin secretion in epilepsy or after seizure activity, blood ghrelin levels are shown decreased both in experimental epileptic rodents and in humans. Therefore ghrelin results as a neuroprotective agent, exerting antiepileptic, antioxidant and anti-inflammatory effects on neuronal brain cells. A better understanding of ghrelin's activities may help to develop new therapeutic approaches to epilepsy, the most common neurological problem worldwide and, in particular, to refractory seizure forms.

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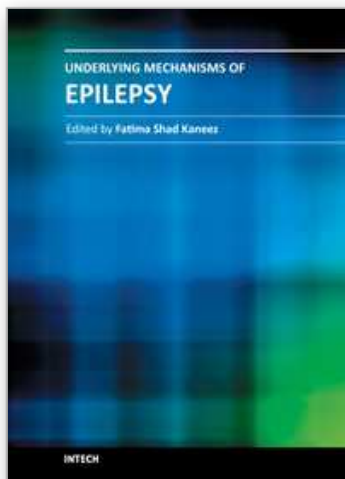
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This book is a very provocative and interesting addition to the literature on Epilepsy. It offers a lot of appealing and stimulating work to offer food of thought to the readers from different disciplines. Around 5% of the total world population have seizures but only 0.9% is diagnosed with epilepsy, so it is very important to understand the differences between seizures and epilepsy, and also to identify the factors responsible for its etiology so as to have more effective therapeutic regime. In this book we have twenty chapters ranging from causes and underlying mechanisms to the treatment and side effects of epilepsy. This book contains a variety of chapters which will stimulate the readers to think about the complex interplay of epigenetics and epilepsy.

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