



Serum Ghrelin Level in A Sample of Egyptian Epileptic Patients

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالَ

لَسْبَدَانِكَ لَا عِلْمَ لَنَا
إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ
الْعَلِيمُ الْعَظِيمُ

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List of Abbreviations

Abb.	Full term
2-AG	2-arachidonoyl-glycerol
ACTH	Adrenocorticotopic hormone
AED	Anti-epileptic drug
AEG	Antiepileptogenesis
AgRP	Agouti-related protein
BRE	Benign rolandic epilepsy
COX-2	Cyclooxygenase-2
EEG	Electroencephalography
EIA	Enzyme Immunoassay
EPSPs	Excitatory postsynaptic potentials
ERK	Extracellular signal-regulated kinase
GHS-R	Growth hormone secretagogue receptor
GnRH	Gonadotropin-releasing hormone
GOAT	Ghrelin O-acyltransferase
HPA	Hypothalamic pituitary adrenal
IL-1 β	Interleukin-1beta
NPY	Neuropeptide Y
NREM	Non rapid eye movement
PSs	Population spikes
PTZ	Pentylenetetrazol
REM	Rapid eye movement
SRSs	Spontaneous recurrent seizures
SUDEP	Sudden unexplained death in epilepsy
TNF- α	Tumor necrosis factor alpha
VPA	Valproic acid

INTRODUCTION

Epilepsy is a group of neurological disorders characterized by epileptic seizures (*Chang et al., 2003*).

The cause of most cases of epilepsy is unknown (**Epilepsy Fact sheet, 2016**). Some cases occur as the result of brain injury, stroke, brain tumors, infections of the brain, and birth defects, through a process known as epileptogenesis (*Goldberg and Coulter, 2013*).

Epileptic seizures are the result of excessive and abnormal nerve cell activity in the cortex of the brain (*Fisher et al., 2005*).

Childhood with centro-temporal spikes, also known as rolandic epilepsy, is common and easy to diagnose by history and a typical electroencephalography (EEG) signature epilepsy. Most patients do not require treatment and cognitive outcome is good, but some are at risk for learning and behavioral difficulties (*Currie et al., 2017*).

Rolandic epilepsy can serve as ‘dissection scissors’ for further analyzing complex cognitive skills crucial for academic achievement, such as reading comprehension at the text instead of word level. (*Currie et al., 2017*).

This is well illustrated by a study which tried to tease out the contribution of abilities such as listening comprehension, word reading (accuracy and rate), and non-verbal reasoning to

reading comprehension. As expected, performances of patients as a group were lower than controls, but only mildly and with heterogeneous scores (*Currie et al., 2017*).

A handful of children had significant impairments; this may be diversely explained by comorbidities, such as attention-deficit–hyperactivity disorder or a history of a previous speech and language disorder, as well as a more sustained interictal epileptic activity or an antiepileptic medication (*Currie et al., 2017*).

Ghrelin is the "hunger hormone", is a peptide hormone produced by ghrelinergic cells in the gastrointestinal tract (*Sakata and Sakai 2010*) which functions as a neuropeptide in the central nervous system (*Dickson et al., 2011*).

Besides regulating appetite, ghrelin also plays a significant role in regulating the distribution and rate of use of energy (*Burger and Berner, 2014*).

Ghrelin also activates the cholinergic–dopaminergic reward link in inputs to the ventral tegmental area and in the mesolimbic pathway (*Naleid et al., 2005*).

Ghrelin injections increase an animal's motivation to seek out food, behaviors including increased sniffing, foraging for food, and hoarding food. (*Naleid et al., 2005*).

Studies have shown that ghrelin levels are negatively correlated with weight. This data suggests that ghrelin functions as an adiposity signal, a messenger between the body's energy stores and the brain (*Schwartz et al., 2000*).

Ghrelin has been shown to be a factor in sleep regulation in humans. In a study in which healthy young males were given ghrelin, the time spent in slow-wave sleep increased overall during the night and non-rapid-eye-movement (NREM) sleep was increased during the night. Stages of sleep are also related to patterns of seizure occurrence (**Bazil, 2003**).

Epileptiform EEG discharges probably multiply during NREM sleep, given that seizures generally emerge in the NREM sleep (**Naleid et al., 2005**).

In patients with epilepsy, sleep disorders are common, but they are diverse and complex. A connection between sleep and epilepsy has long been established and it has been shown that physiologic changes involved in the non-rapid-eye movement (NREM) sleep are associated with increased susceptibility to seizures (**Naleid et al., 2005**).

AIM OF THE WORK

1. To investigate the role of ghrelin in Rolandic Epilepsy.
2. To study any possible correlation between serum ghrelin level and clinical parameters as age ,sex , frequency of fits , learning performance of the selected cases and controls ,effect of antiepileptic drugs on serum ghrelin level .

Chapter 1

EPILEPSY

Epilepsy is a neurologic condition that affects people of all ages and has no geographic, social, or racial boundaries (*Sander, 2003*).

The operational revised 2014 definition of epilepsy by the International League Against Epilepsy is (*Fisher et al., 2014*):

1. At least 2 unprovoked (or reflex) seizures occurring greater than 24 hours apart.
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after 2 unprovoked seizures, occurring over the next 10 years.
3. Diagnosis of an epilepsy syndrome.

A seizure is defined as a transient change in the clinical state of the patient due to excessive neuronal firing or depolarization. Seizures can be provoked or unprovoked (*Singh & Trevick, 2016*).

A seizure can have motor, sensory, psychic, or autonomic manifestations or a combination of these.

Examples of evidence that increases the probability of having additional seizures include:

1. Epileptiform activity on EEG or
2. A potential epileptogenic abnormality on brain imaging.

Thus, if the clinical picture, EEG or imaging findings increase the probability of another seizure to $\geq 60\%$, then these individuals are defined as having epilepsy, and should be, as clinically they are statistically equivalent in their recurrence risk to those who have had two or more unprovoked seizures (*Fisher et al., 2014*).

Epilepsy is considered “resolved” under the following circumstances:

1. In a patient with an age-dependent epilepsy syndrome who is older than the age in which this syndrome is active, or
2. A patient who has been seizure free for ≥ 10 years and has been off all anti-seizure medications for ≥ 5 years.

Treatment decisions must be individualized. The changes made in 2014, as outlined above, compared to the prior definition from 2005, align the definition and resolution of epilepsy with clinical practice (*Ngugi et al., 2010*).

▪ **Incidence:**

According to a recent study, 70 million people have epilepsy worldwide and nearly 90% of them are found in developing regions (*Ngugi et al., 2010*).

Globally, an estimated 2.4 million people are diagnosed with epilepsy each year (*Ngugi et al., 2010*).

The prevalence of epilepsy in developed countries ranges from 4 to 10 cases per 1000. Studies in the developing and tropical countries have reported higher prevalence rates of epilepsy, ranging from 14 to 57 cases per 1000 persons (*Burneo et al., 2005; Carpio & Hauser, 2009*).

Higher prevalence rates of epilepsy in the developing countries is probably related to the methodological aspects of those studies, although in some regions in the world, specific infectious diseases, such as neurocysticercosis, are frequent causes of epilepsy (*Ndimubanzi et al., 2010*).

In developed countries, the incidence of epilepsy exhibits a U-shaped curve, with highest rates in the children and the elderly. In comparison, the incidence of epilepsy seems to peak in early adulthood in developing countries (*Singh & Trevick, 2016*).

▪ **Risk factors:**

There are many known risk factors for epilepsy, which range from head injuries at birth to those at any age, to

chromosomal/genetic syndromes and various inborn errors of metabolism, CNS tumors, stroke or infections and so forth (*Singh & Trevick, 2016*).

The relative risk of developing epilepsy with different conditions in different populations is not known. Epilepsy resulting from infection is a major cause of morbidity and mortality in low-income countries and the most preventable cause of epilepsy worldwide (*Singh & Trevick, 2016*).

Patients may present with seizures during the acute encephalitic process but more often develop neurologic disability, including epilepsy (*Singh & Trevick, 2016*).

▪ **Epilepsy etiology:**

The ILAE Task Force has defined six etiologic categories, focusing on those etiologies with management implications. These categories are:

1. Structural
2. Genetic
3. Infectious.
4. Metabolic.
5. Immune.
6. Unknown.