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ASSAY KITS FOR METABOLIC SYNDROME RESEARCH

01 Large range of biomarkers

02 Ready-to-use assay kits

03 Key player in Ghrelin assay kits

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From metabolic syndrome to cachexia: what's new about metabolic biomarkers ?

By Odile Viltart and Virginie Tolle, PhD - INSERM UMR894 – Centre de Psychiatrie et Neurosciences, Paris, FRANCE

Metabolic syndrome (MetS) is the constellation of risks namely abdominal obesity, insulin-resistance, type 2 diabetes, dyslipidemia and arterial hypertension. In the late 90's the World Health Organisation (WHO) gave a definition of the MetS to better understand mechanism and therefore tempt to find appropriate treatment. Starting with that first definition (initial one) of the metabolic syndrome a range of alternative definitions was suggested. The most widely accepted definition was formulated by EGIR (European Group for the Study of Insulin Resistance) and NCEP (USA National Cholesterol Education Panel).

History of metabolic syndrome

In the early 1920s, the Canadian Surgeon Frederick Banting[1] extracted a compound they named insulin from the islets of Langerhans in the pancreas. When injected into diabetic dogs, the compound decreased the levels of sugar in the dogs' blood and urine. The discovery, coupled with the purification of insulin, helped transform childhood diabetes from a fatal disease to a chronic illness.

By the 1930s, it had become common to classify people with diabetes according to how they reacted to an injection of insulin: insulin-sensitive or type 1 diabetes and insulin-insensitive or type 2 diabetes. Type 2 diabetes accounts for at least 90% of all the cases of diabetes and refers to adults over 40. This type of diabetes is characterised by insulin resistance, a phenomenon by which an individual's body issues have a diminished response to insulin, causing the body to produce larger quantities of insulin to maintain normal blood glucose level.

In the 1980s, insulin resistance had become a major field of research, as physicians began to understand it not only has preconditional of type 2 diabetes, but as also associated with pathological cluster such as obesity, heart disease, stroke and environment that can be named MetS.

Biomarkers[1bis] for the diagnosis and prognosis of nutritional or metabolic disorders

Worldwide, over 70 million people suffer from eating disorders.

Obesity[2] and diabetes are amongst the greatest public health issues for this century. Indeed, over the last 30 years, obesity has more than doubled, achieving **1.5 billion persons**. It does affect without any distinction all the population (children, adult, elderly people) and all socioeconomic status. Obesity is a complex condition which poses a major risk for serious diet-related, non-communicable diseases, including type 2 diabetes.

In the past 20 years, the rates of obesity have tripled in developing countries that have been adopting a Western lifestyle involving decreased physical activity and overconsumption of cheap, energy-dense food.

About 18 million people die every year from cardiovascular disease, for which diabetes and hypertension are major predisposing factors.

Today, more than **1.1 billion adults** worldwide are overweight, and **312 million of them are obese.**

The increase in the prevalence of type 2 diabetes is closely linked to the upsurge in obesity. About 90% of type 2 diabetes is attributable to excess weight.

Consequently, diabetes is rapidly emerging as a global health care problem that threatens to reach pandemic levels by 2030; the number of people with diabetes worldwide is projected to increase from 171 million in 2000 to 366 million by 2030.

Anorexia nervosa (AN)[3]. Amongst eating disorders, Anorexia Nervosa (AN) is characterized by a chronic undernutrition state and a body mass index below 17 [4]. It affects 1-4% of women in the United States and is the leading cause of death among adolescents in Europe.

[1] **Frederick Banting** is the Nobel Prize in Physiology or Medicine 1923

[1bis] **Biomarker** refers to a measurable indicator of some biological state or condition. They can be measured as an objective indicator of a physiological or pathological state or responses to a therapeutic intervention. Biomarkers may be used for personalized therapeutic either as diagnosis, predictive (likely benefit from a treatment) or prognostic (likely outcome of a specific treatment) tool.

[2] **Obesity** is characterized by an excess fat mass due to an imbalance between energy intake and energy expenditure. Beyond nutrition and genetics, environmental factors may be involved in the development and installation of obesity. Obesity is often associated with increased risk of developing type 2 diabetes, cardiovascular problems and certain cancers.

[3] **Anorexia nervosa** is an eating disorder characterized by a low body weight, fear of gaining weight and undernutrition resulting from self-imposed starvation. There is evidence for biological, psychological, developmental, and sociocultural risk factors, but the exact cause of eating disorders is unknown (*Rikani et al.*).

[4] **Body mass index** (BMI = calculated as body mass in kg divided by the length in m^2) is used as an indicator of the level of severity in patients with overweight or anorexia nervosa. It corresponds to Severity in overweight: 1) overweight (25<BMI<30), 2) Moderate (30<BMI<35), 3) Severe (35<BMI<40), 4) Massive (BMI>40) (Data INSERM) - Severity in anorexia nervosa 1) Mild (BMI>17, 2) Moderate (16<BMI<17), 3) Severe (15<BMI<16), 4) Extreme (BMI<15) (*Peat et al.*)

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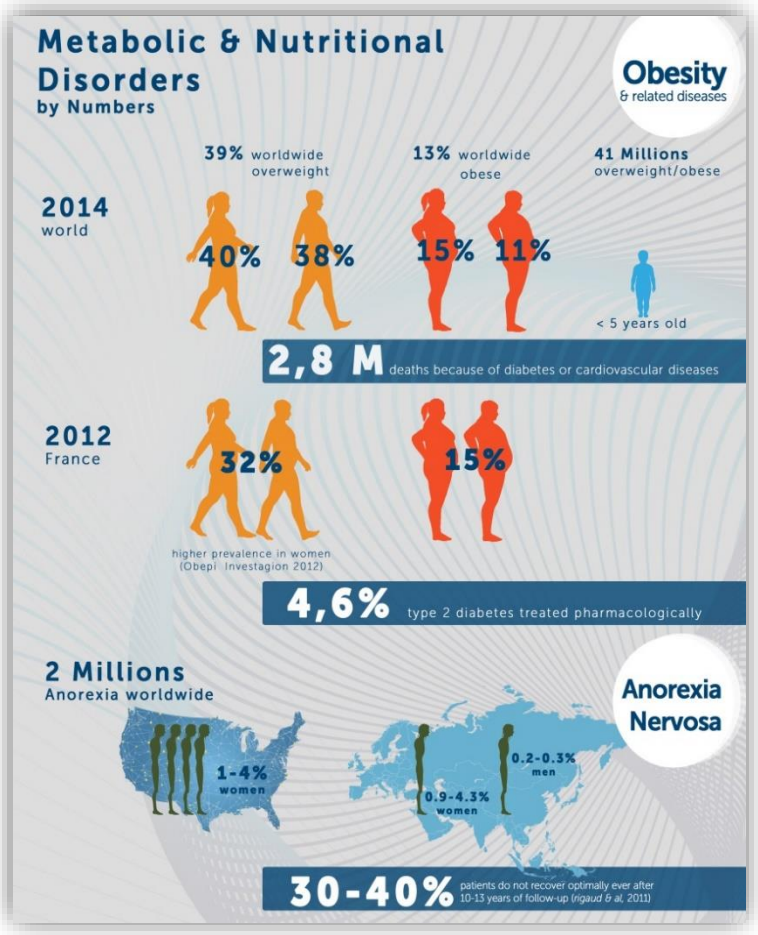
Globally, AN affects about two million people (*Global burden of disease study 2013*). It is estimated to occur in 0.9% to 4.3% of women and 0.2% to 0.3% of men in Western countries at some point in their life (*Smink et al. 2012*). 30 to 40% of patients do not recover optimally even after 10 to 13 years of follow-up (*Rigaud et al., 2011).*

The exponential increase of nutritional and metabolic diseases induced by a disequilibrium between the energy input and expenditure, *i.e.* too much, too less, or energy expenditure (such as obesity or anorexia) generates care expenses that become a real health societal problem. Indeed, such an important cost can be explained by chronicity, severity and usually a lack of appropriate treatment. It would be reduced by an early diagnosis of the disease using relevant **biomarkers** or **biological markers** that might lead to begin the treatment at an early stage of the disorder. Thus, it is necessary to find pertinent biological markers, **easy to measure,** to evaluate the early phase and the different stages as well as the severity of the disease to propose to the patient pertinent-personalized therapeutic strategies.

With the identification these past 20 years of new regulators of energy homeostasis in the brain or peripheral organs, potential new **biomarkers for metabolic** or **nutritional disorders** are proposed.



A special focus is made on hormones produced in the adipose tissue or gastrointestinal tract since they are secreted in the blood and signal to the brain about the nutritional or metabolic status. The absence of very **specific** and **sensitive immunoassays** is considered to be a limitation to the appropriate measurement of these biomarkers. However, these past years, new technological developments and their effects in immunoassays alleviate such a downside.

Which biomarkers?

There is an urgent need to identify specific biological markers

To date, there is no effective pharmacological treatment that can guarantee a complete nutritional recovery in patients suffering from these diseases. In order to develop new therapeutical strategies and determine new candidate strategies for treatment, there is an urgent need to identify specific biological markers that could be involved in the maintenance and/or worsening of the disease.

These past years, the scientific community has identified specific biomarkers that are dysregulated in the overnutrition or undernutrition states and can also reflect the type (anorexia nervosa *versus* obesity) or subtype (bingeing-purging *versus* restrictive AN) of the disease (*Germain et al.*, 2010; *Germain et al.*, 2016) as well as its severity or duration (*Terra et al.*, 2013).

Past and current research focuses on investigating endocrine biomarkers produced by the adipose tissue or gastrointestinal tract, such as **leptin** (*Legroux-Gérot et al.*, 2009; Jamar *et al.* 2016), **adiponectin** (*Terra et al.*, 2013; Lopez-Jaramillo *et al.*, 2014), **ghrelin** and **obestatin** (*Gorwood et al.*, 2016; *Germain et al.*, 2010; *Kuppens et al.*, 2015) or **26-RFa** (*Galusca et al.*, 2012) in AN and obesity.

To better understand the mechanisms involved in the process of malnutrition/renutrition, identification of biomarkers predictive of successful refeeding in patients or animal models mimicking certain aspects of the disease is needed.

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Beyond AN, applications for other diseases associated with undernutrition, such as cachexia or malnutrition worldwide. Ghrelin and leptin, as well as other adipocytokines such as resistin or adiponectin, are also investigated as potential biomarkers to diagnose cachexia and predict survival in cancer patients (*Mondello et al.*, 2014, *Kerem et al.*, 2008).

Obesity – anorexia/cachexia: two faces of a same neurobiological circuit?

The actions of these biomarkers on ***homeostatic*** and ***non-homeostatic neuronal circuits*** regulating eating behaviors begin to be well described and better understood (*Morton et al., 2014*, Fig. 1- page 5). Peripheral hormones reach the brain through specific way of transport across the blood brain barrier (*Schaeffer et al., 2013*) targeting different brain areas involved in the homeostatic and non-homeostatic regulation of food intake, energy expenditure and thus body weight.
Briefly, hypothalamus and brainstem structures (*nucleus tractus solitarius*) are direct sensors of the energy and metabolic balance while the meso-cortico-limbic system (ventral tegmental area – *nucleus accumbens*) is devoted to the motivational/rewarding aspects of the food. Obesity and Anorexia Nervosa display deregulation in the synthesis and/or release of several peripheral factors that modulate central feeding centers. In particular, plasma ghrelin and leptin concentrations show opposite variations leading to the hypothesis of a key role of these hormones in the physiopathology of these diseases (from the genesis to the different outcomes inherent to such feeding disorders).

A better understanding of their evolution/kinetic during the course of the disease is essential to potentially find a pertinent therapeutic solution by acting at different levels to reprogram a dysfunctional system. Such fundamental studies, using genetically-engineered mice (total deletion or conditional deletion of genes in specific neuronal or peripheral population) have permitted to highlight the role of gut hormones and/or central neuromediators (like dopamine and serotonin, for example). The mechanisms of action leading to a chronicisation of the disease (obesity or anorexia) remain currently poorly understood rendering urgent to perform valuable and reproducible measurements of the evolution of pertinent biomarkers during the course of the disease to better understand the mechanisms of action of these hormonal biomarkers in pathological states at both central and peripheral levels.

Bertin Technologies is now well recognized for its expertise to develop analytical tools to measure such biomarkers. Their use as either diagnostic or prognostic biomarkers in human subjects in pathological states and in parallel to follow their evolution in animal models might be essential to assess clinical vs fundamental research. In this view, Bertin Technologies offers the possibility to propose immunoassays specific for each species and to further develop specific pharmacological blockers and enhancers.

[5]CMME : Centre des Maladies Mentales et de l'Encéphale (Sainte-Anne Hospital, Paris)

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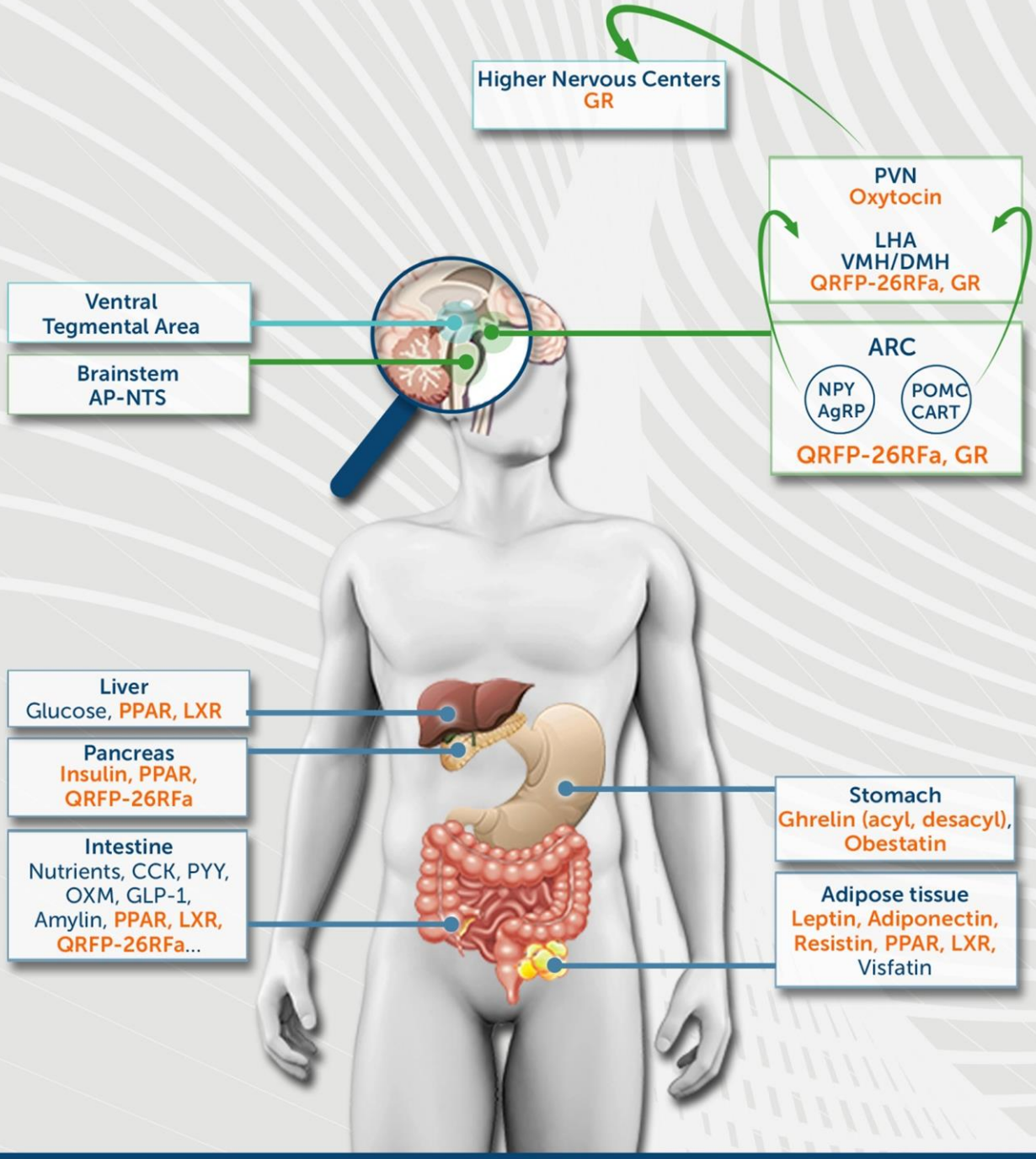
Representation of both central structures and peripheral factors involved in the regulation of energy metabolism and food intake

Figure 1



The brain areas involved in the homeostatic regulation of energy metabolism and food intake are depicted in green. Peripheral signals that are released in the blood access circumventricular organs such as the median eminence in order to directly target orexigenic (NPY, AgRP) and anorexigenic (POMC, CART) neuronal populations within the hypothalamic arcuate nucleus. These signals can also directly target the *nucleus tractus solitarius* through another circumventricular organ, the *area postrema*, or *via* the vagus nerve.
The brain structures involved in the non-homeostatic regulation of food intake are depicted in turquoise. The ventral tegmental area that controls the rewarding aspects of feeding behavior contains dopaminergic neurons which express leptin and ghrelin receptors. In green/turquoise, the higher nervous centers responsible of the integration of non homeostatic and homeostatic information to drive individuals to an adapted feeding behavior.

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New biomarkers for future personalized therapeutic treatments
Our own experience using Bertin Bioreagent kits

These past years, our research has been focused on understanding the role of preproghrelin, a complex prohormone encoding various peptides (acyl and desacyl ghrelin, obestatin) with structural and functional heterogeneity, in the pathophysiology of eating disorders. Our aim was to evaluate the relative ratio of these peptides in undernutrition conditions in both rodents and humans. The absence of selective and reliable assays to measure all three ghrelin-derived in the same biological sample was a limitation to understand how these key gastrointestinal peptides were regulated in pathological conditions.
First, we validated **Bertin Bioreagent's** immunoassay kits by demonstrating the absence of immunoreactivity for both acyl and desacyl ghrelin in preproghrelin deficient mice (*Hassouna et al. 2014*). Since immunoassays kits have been developed in multi-species, we are able to use them for explorations in different models: rat, mouse, human. Thus, we were able to assay ghrelin in both obesity (*Lacroix et al. 2015*) and undernutrition states in both animal models (*Méquinion et al. 2015*) and AN patients in collaboration with members of the interdisciplinary network on eating disorders, GIR-AFDAS-TCA (*www.anorexieboulimie-afdas.fr*) and CMME[5] (Paris, France). Exploration of these biomarkers in preclinical and clinical studies is essential to better understand the pathophysiology of the disease. In collaboration with **Bertin Technologies**, we have worked on optimizing the conditions of sampling, treatment and storage of samples.

Such assays have several advantages:

- they are developed in multi-species, from rodent (rat and mouse) to human, which is ideal for preclinical to clinical investigations,
- they are specific for different isoforms of the same peptide (such as acyl *versus* desacyl ghrelin) that can have various biological effects (*Delhanty et al. 2013*),
- they are sensitive enough to detect small concentrations or variation ranges,
- they are reproducible and designed to recover peptides with post-translational modifications (such as acylation) with specific treatment.

What treatment(s) for tomorrow?

Identify biomarkers is a crucial step

Lifestyle modification is the mainstay of prevention and treatment for metabolic syndrome and type 2 diabetes; however, it can be costly and labour-intensive. Pharmacotherapy is considered as second line of therapy in adults, but its use in children is controversial. In that framework, the use of specific **biomarkers** is fundamental to better apprehend the mechanisms that are involved in eating disorders and regulation of body weight. The future will be to use targeted and personalised therapies. Indeed, the generalisation of genetic, epigenetic, or pharmacogenetics tools will be of importance to know the ins and outs of the disorders related to food intake according to age, sex and endocrine disruptors.

The current scientific priorities include more specifically the study of (i) the interaction between genes and environment with a special focus on the role of the gut microbiota and the impact of various environmental pollutants and (ii) the dialog between the brain and the gut. Recent data obtained by the French consortium Micro-Obes (2013)[6] have shown that individuals with a poor gut bacteria diversity are exposed to a higher risk to develop complications linked with an obese phenotype. Changing the composition of the daily diet was sufficient to restore a normal gut microbiota. Thus, the development of an easy test to specifically identify these "at risk" persons may help to propose an adapted and personalized treatment.

In this view, identifying biomarkers is a necessary step for achieving better diagnostics and follow evolution of diseases and efficiency of treatments. The development of new valuable preclinical models (*in vivo* and/or *in vitro*) to further assess the mechanisms and the impact of new potential treatments is fundamental to obtain substantial knowledge and answers in the field of type II diabetes, nutrition and metabolic disorders. Such data might be obtained through dedicated clinical platforms to phenotype and follow up large national cohorts.

[6]http://unice.fr/faculte-de-medecine/actualite/toute-actualite/doc-2014-2015/journal-nutrition-def.pdf

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HUNGER HORMONE ASSAY KITS

Bertin Technologies develops, manufactures and distributes its own assay kits under the Bertin Bioreagent's brand name (formerly known as SPI-Bio). We also offer you very high quality assay kits from Cayman Chemical and INDIGO Bioscience companies.

ADIPONECTIN: THE STRATEGIC TARGET FOR METABOLIC SYNDROME

Adiponectin *is a 244 amino-acid protein hormone produced mainly by adipocytes of the adipose tissue. Adiponectin is a hormone mainly influencing the metabolism of saccharides and lipids, increasing the sensitivity of tissues to insulin. Its effect leads to an increased transport and utilization of glucose and free fatty acids in muscles, liver and adipose cells.*

➢ **Adiponectin (human) ELISA kit** **Cat No: A05185**
- Recognize natural and recombinant adiponectin
- All reagents provided are ready to use
- Working range fits with physiological concentration

➢ **Adiponectin High Sensitivity (human) ELISA kit** **Cat No: A05186**
- Highly sensitive
- Many samples have been validated
- Small volume of sample size

➢ **Adiponectin (mouse) ELISA kit** **Cat No: A05187**
- 41 samples in one shot
- Cross-react partly with rat adiponectin
- Supplied with internal quality control

AFABP: A FATTY ACID TRAFFICKING ACTOR

Adipocyte Fatty Acid Binding Protein (AFABP) *is a 15 kDa member of the intracellular Fatty Acid Binding Protein (FABP) family. It is expressed in a tissue specific manner in differentiated adipocytes. It is a critical gene in the regulation of the biological function of these cells. According to some results, AFABP may be involved in mediating obesity-induced alterations in adipocyte gene expression.*

➢ **A-FABP (human) ELISA kit** **Cat No: A05181**
- New marker for atherosclerosis & metabolic syndrome
- Provided with internal quality control
- Involved in cholesterol accumulation

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GHRELIN: THE HUNGER HORMONE

Ghrelin *gene raises to mRNA prepro-ghrelin of 117 amino acids. This precursor is processed into ghrelin, 28 amino acids (human). This endogenous peptide appears directly related to feeding behavior. Its potential therapeutic importance may also be involved in cardiovascular, gastrointestinal, muscle mass maintenance, infertility, cachexia and cancer.*

Bertin Technologies offers you an exclusive range of bioanalytical tools to assay Acylated and Unacylated Ghrelin with very high sensitivity whatever their collection procedure.
Bertin Technologies has a solution, from early discovery programs using our 384-well plate format to select your GOAT inhibitor, to pre-clinical or clinical stages.

➢ **Large range of Ghrelin assays**
- *Measure acylated and unacylated ghrelin*
- *Ubiquitous*
- *Matrices: plasma, serum & cell culture supernatant*

Cat No	Designation	Application
A05106.96 wells	Acylated Ghrelin (human) Express ELISA kit	PHMB, PMSF, Aprotinin samples
A05106.384 wells	Acylated Ghrelin (human) 384w ELISA kit	GOAT inhibitor screening
A05117.96 wells	Acylated Ghrelin (mouse, rat) Express ELISA kit	PHMB, PMSF, Aprotinin samples
A05118.96 wells	UnAcylated Ghrelin (mouse, rat) Express ELISA kit	PHMB, PMSF, Aprotinin samples
A05119.96 wells	UnAcylated Ghrelin (human) Express ELISA kit	PHMB, PMSF, Aprotinin samples
A05306.96 wells	Acylated Ghrelin (human) Easy Sampling ELISA kit	Any kind of sample
A05317.96 wells	Acylated Ghrelin (mouse, rat) Easy Sampling ELISA kit	
A05318.96 wells	UnAcylated Ghrelin (mouse, rat) Easy Sampling ELISA kit	
A05319.96 wells	UnAcylated Ghrelin (human) Easy Sampling ELISA kit	
A05320.96 wells	UnAcylated Ghrelin (dog) Easy Sampling ELISA kit	
A05321.96 wells	Acylated Ghrelin (dog) Easy Sampling ELISA Kit	
A05401.96 wells	Acylated Ghrelin (pig) ELISA kit	PHMB, PMSF, Aprotinin samples
A05402.96 wells	UnAcylated Ghrelin (pig) ELISA kit	PHMB, PMSF, Aprotinin samples
D31009	Sampling Tubes with PHMB	Sample preparation

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INSULIN: LOWERING GLUCOSE RATE

Insulin *is a polypeptide hormone with molecular weight of 6,000 Daltons, composed of two peptides chains jointed by two cross-linked disulphide bonds and synthesised by the beta cells of the islets of Langherans. Its best known action is to lower the blood glucose concentration by increasing the rate at which glucose is converted into glycogen in the liver and muscles, and to fat in adipose tissue.*
Focus on hemolysis*: hemolysis interferes with the assay by degrading insulin.*
To prevent hemolysis consequences, Bertin Bioreagent has an inhibitor cocktail and a procedure available

- **Insulin (mouse, rat) ELISA kit 96 wells / 480 wells** — **Cat No: A05105**
  - Ubiquitous
  - Use with hemolysed samples
  - Matrices: plasma & serum

- **Insulin (human) ELISA KIT** — **Cat No: A05322**
  - Broadest Standard Curve Range
  - High sensitivity
  - Versatile assay for all your samples

LEPTIN: A SATIETY HORMONE

Leptin*, the product of the obese gene, is produced mainly in the adipose tissue, and is considered to play an important role in appetite control, fat metabolism and body weight regulation. Leptin has a dual action: it decreases the appetite and increases energy consumption. Leptin is secreted in circadian fashion with nocturnal rise in both lean and obese patients.*

- **Leptin (human) ELISA kit** — **Cat No: A05174**
- **Leptin (mouse, rat) ELISA kit** — **Cat No: A05176**
- **Leptin Receptor (human) ELISA kit** — **Cat No: A05175**

- New marker for atherosclerosis & metabolic syndrome
- Provided with internal quality control
- Involved in cholesterol accumulation

GROWTH HORMONE: TRAIN HARD AND SLEEP WELL

Growth Hormone (GH) *is a polypeptide hormone with a molecular weight of 23 K Daltons released from somatotropes of the anterior pituitary. It is regulated by several neurotransmitters and neuropeptides. Amongst other functions, it plays an essential role in regulating body growth.*

- **Growth Hormone (rat) ELISA kit** — **Cat No: A05104**
  - Less that 1 hour bench time
  - Matrices: Plasma, serum & culture supernatant
  - Highly sensitive

QRFP-26RFA: INSULIN ENHANCER

QRFP-26RFa *is a neuropeptide of 26 amino acids from the RFamides family. It is mainly produced in the hypothalamus and in some peripheral tissues like the brainstem or the lateral horns of the spinal cord. QRFP-26RFa has an action on the regulation of the high fat diet and on the lipolysis in adipocyte of obese individuals.*

- **QRFP-26RFa (human) ELISA kit** — **Cat No: A05037**
  - Exclusive assay
  - New biomarker
  - Sensitive

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HUNGER HORMONE ASSAY KITS

RESISTIN: A CREDIBLE LINK BETWEEN INSULIN RESISTANCE AND TYPE 2 DIABETES

Resistin *is a peptide hormone belonging to the class of cysteine-rich secreted proteins which is termed the RELM family. It is described as ADSF (Adipose Tissue-Specific Secretory Factor) and FIZZ3 (Found in Inflammatory Zone).*
Studies have shown that in mice, resistin impairs glucose tolerance and insulin action. It also inhibits adipogenesis in murine 3T3-L1 cells. Therefore, resistin has been proposed as an adipocyte secreted factor that is thought to link obesity and type 2 diabetes.

- **Resistin (human) ELISA kit** — **Cat No: A05177**
  - Matrices: human serum, plasma and culture supernatant
  - Assay 41 samples in duplicate
  - Incubation: 3 x 1 hour

- **Resistin (mouse) ELISA kit** — **Cat No: A05178**
  - Matrices: mouse serum, plasma and culture supernatant
  - Assay 40 samples in duplicate
  - Incubations: 2 x 1 hour | 30 minutes

- **Resistin (rat) ELISA kit** — **Cat No: A05179**
  - Matrices: mouse serum, plasma, and culture supernatant
  - Assay 40 samples in duplicate
  - Incubations: 2 x 1 hour | 30 minutes

OBESTATIN: SHED LIGHT ON THE DARK SIDE OF THE OBESTATIN

Obestatin *is an amidated peptide made of 23 amino-acids with a secondary conformation in alpha-helix. Obestatin was identified as an anorexigenic peptide with an action on the food intake. First studies shown that the obestatin reduced food intake and body weight. It can be considered as an antidiabetic peptide by positively influencing glucose and lipid metabolism.*

- **Obestatin (human) ELISA kit** — **Cat No: A05036**
- **Obestatin (mouse, rat) ELISA kit** — **Cat No: A05035**
  - Less that 1 hour bench time
  - Matrices: plasma, serum & culture supernatant
  - Sample volume: 50 µL

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Acronyms – figure 1 – page 5

AgRP: Agouti Related Protein;
ARC : *arcuate nucleus*;
AP: *area postrema*;
CART: Cocaïne Amphetamine Related Transcript;
CCK: Cholescystokinin;
DMH : Dorsomedial Hypothalamic nucleus;
GLP-1: Glucagon-Like Peptide -1;
GR: Glucocorticoïd receptor;
LHA :Lateral Hypothalamic Area;
LXR: Liver X receptor;
NPY : Neuropeptide Y;
NTS: *Nucleus Tractus Solitarius*;
POMC :Proopiomelanocortin;
PPAR: Peroxisome Proliferator-Activated Receptor;
PYY: Peptide YY
OXM: Oxytomodulin;
QRFP-26RFa: 26 amino-acid RF(Arg-Phe)amide;
VMH: Ventromedial Hypothalamic nucleus.

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