Osteocalcin

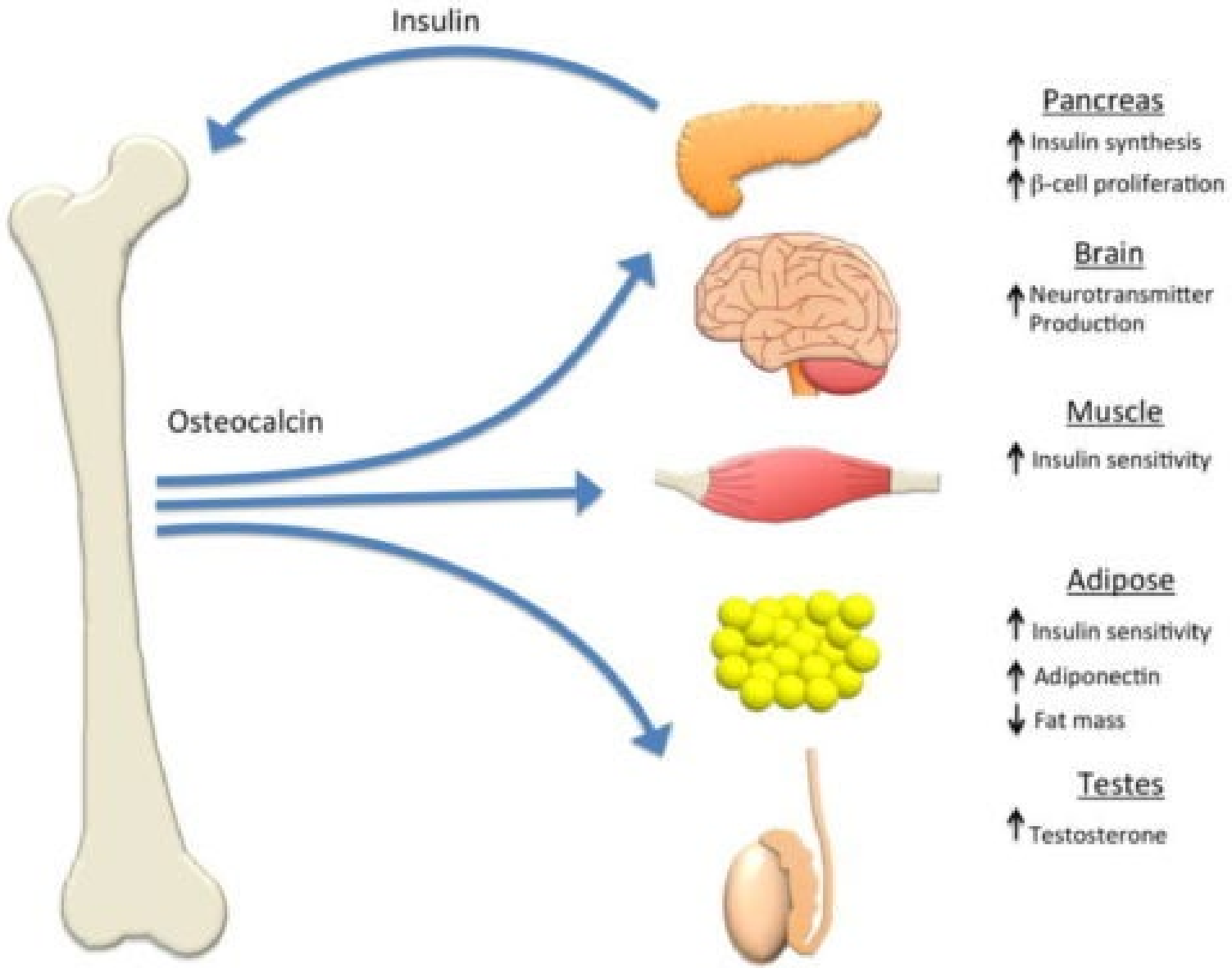
What is osteocalcin?

Osteocalcin is a protein hormone produced by osteoblasts, the cells that build bones. Osteocalcin binds calcium in the bones, working to maintain and regenerate bone tissue.

Studies have found that as a hormone, osteocalcin is also released into the blood, where it:

Increases the production of insulin by the pancreas and adjusts blood glucose levels
Stimulates testosterone production
Increases muscle strength
Improves brain function

The normal range is around 8 – 32 ng/mL.


Insulin
Osteocalcin
Pancreas
↑ Insulin synthesis
↑ β-cell proliferation
Brain
↑ Neurotransmitter Production
Muscle
↑ Insulin sensitivity
Adipose
↑ Insulin sensitivity
↑ Adiponectin
↓ Fat mass
Testes
↑ Testosterone

What is an osteoblast vs an osteoclast?

What is an osteoblast vs an osteoclast?

An osteoblast builds the bone, whereas an osteoclast eats up the bone so that it can be reshaped into a stronger and resilient load-bearing structure.

Low osteocalcin levels usually indicate lower bone turnover.

Osteocalcin can be decreased by:

- Underactive thyroid (Hypothyroidism)
- Underactive parathyroid gland (Hypoparathyroidism)
- Growth hormone deficiency
- Liver disease
- Smoking
- Some drugs, such as glucocorticoids and drugs that slow the progression of bone loss (i.e., antiresorptive agents such as bisphosphonates or hormone-replacement therapy [HRT])

Increasing Osteocalcin and Improving Bone Health

- Weight loss and calorie restriction may or may not affect osteocalcin levels, but overall, weight loss improves bone health in obese and overweight people in general.
- Smoking lowers osteocalcin levels and may slow bone healing.
- Regular exercise increases osteocalcin levels and supports bone health.
- Vitamin K activates osteocalcin and increases its blood levels.
- Vitamin D helps produce osteocalcin in the body and increases bone strength.
- Zinc is important for bone health and may help increase osteocalcin.
- Glucocorticoids are steroid anti-inflammatory drugs that **may reduce osteocalcin levels** and increase the risk of osteoporosis in the long run.

Where else might we find high glucocorticoids affecting osteocalcin?

Higher osteocalcin levels usually indicate higher bone turnover.

Osteocalcin can be increased by:

- Periods of rapid growth (puberty)
- Intense physical exercise
- Bone fractures
- Osteoporosis
- Softening of bones (osteomalacia)
- Vitamin D deficiency
- Overactive parathyroid gland (hyperparathyroidism)
- Overactive thyroid gland (hyperthyroidism)
- Paget disease (a bone remodeling disease)
- Chronic kidney disease (renal osteodystrophy)
- Bone cancer and other cancers that metastasize to the bone
- Excess growth hormone (acromegaly)

Osteocalcin Function & Health Effects

Bone Health

Osteocalcin is responsible for binding calcium to bones, which is what gives bones their strength and flexibility. For this process to occur, osteocalcin first needs to be activated by vitamin K2. However, more osteocalcin is not always a sign of bone strength. **Osteocalcin levels can increase as a result of a widespread bone loss.** In older people, high blood levels of osteocalcin predict lower bone density (particularly in the hip and spine) and fracture risk, including hip fractures.

Osteocalcin Function & Health Effects

Glucose Regulation

Osteocalcin works as a hormone to help adjust insulin and glucose levels in the body.

In the pancreas, osteocalcin increases insulin production and it also increases the number of beta cells that produce, store, and release insulin.

Osteocalcin increases the production of adiponectin in fat cells (adipocytes). Adiponectin, in turn, increases the uptake of glucose into fat and muscle cells.

Low levels of osteocalcin can impair the body's ability to use insulin to control glucose levels.

Osteocalcin Function & Health Effects

Muscle Strength

Osteocalcin increases strength, muscle mass, and exercise capacity. It may prevent muscle wasting and fractures in seniors.

Higher levels of blood osteocalcin have been linked to muscle strength in women over the age of 70. Plus, osteocalcin may reduce the risk of falls and bone fractures by maintaining muscle mass. Indirectly, osteocalcin helps build muscles by increasing testosterone.

Osteocalcin Function & Health Effects

Brain Function

Studies have found that osteocalcin increased the production of monoamine neurotransmitters (dopamine, noradrenaline, and serotonin) in the brains of mice. These neurotransmitters play significant roles in motivation, learning, mood, and memory. What's more, osteocalcin-deficient mice have impaired learning and memory.

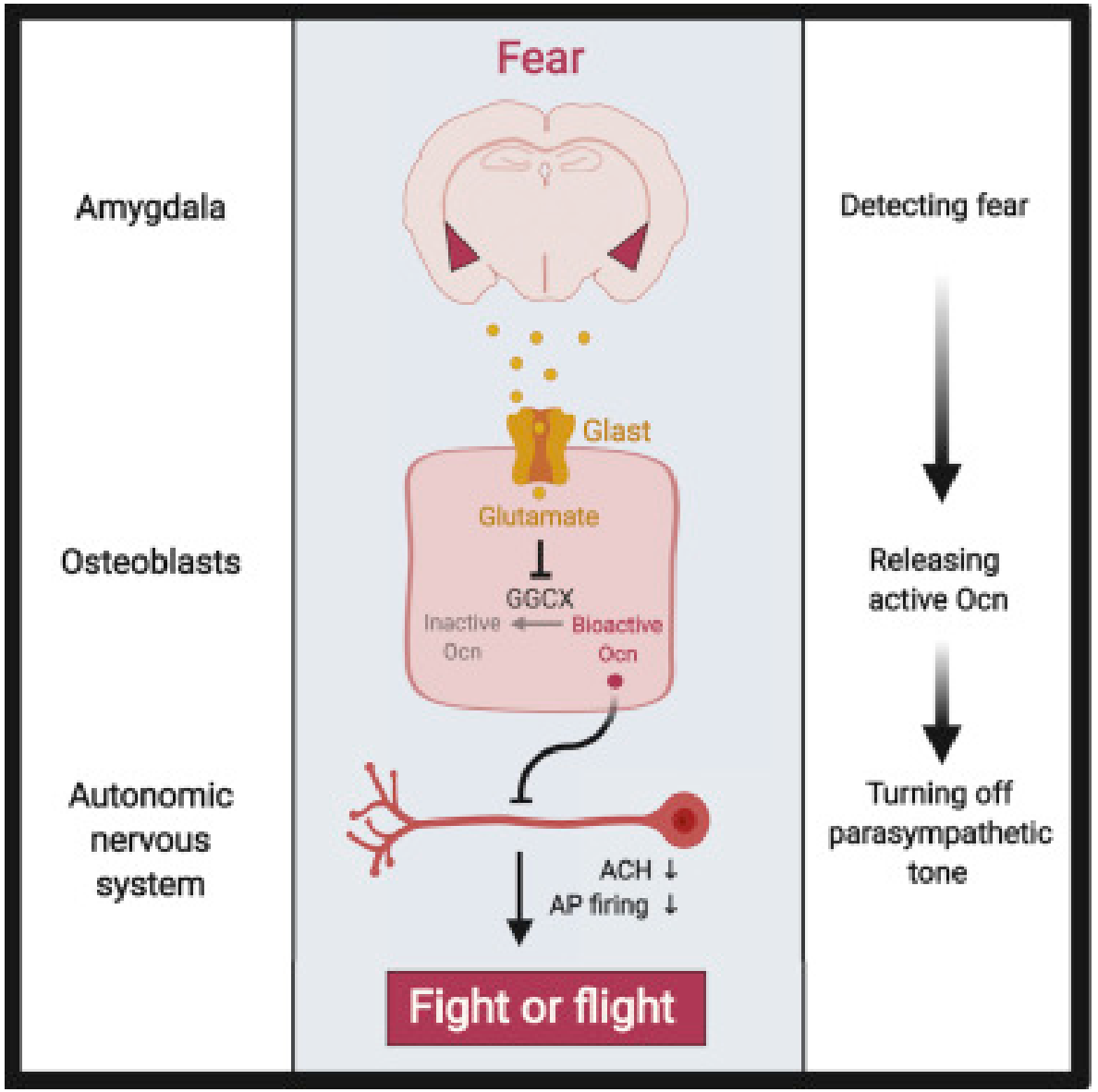
In a human study of 44 people, low osteocalcin levels were linked to negative changes in the microstructure of the brain (in the caudate, hypothalamus, thalamus, putamen, and subcortical white matter) and reduced cognitive performance.

In another study of 117 women between the ages of 71 and 78 years, higher osteocalcin levels were associated with better cognitive function.

Correlation does **NOT** equal causation.

We must continue to explore the relationships within the body.

Acute Stress Response


Fear
Amygdala
Osteoblasts
Autonomic nervous system
Glast
Glutamate
GGCX
Inactive Ocn
Bioactive Ocn
ACH ↓
AP firing ↓
Fight or flight
Detecting fear
Releasing active Ocn
Turning off parasympathetic tone

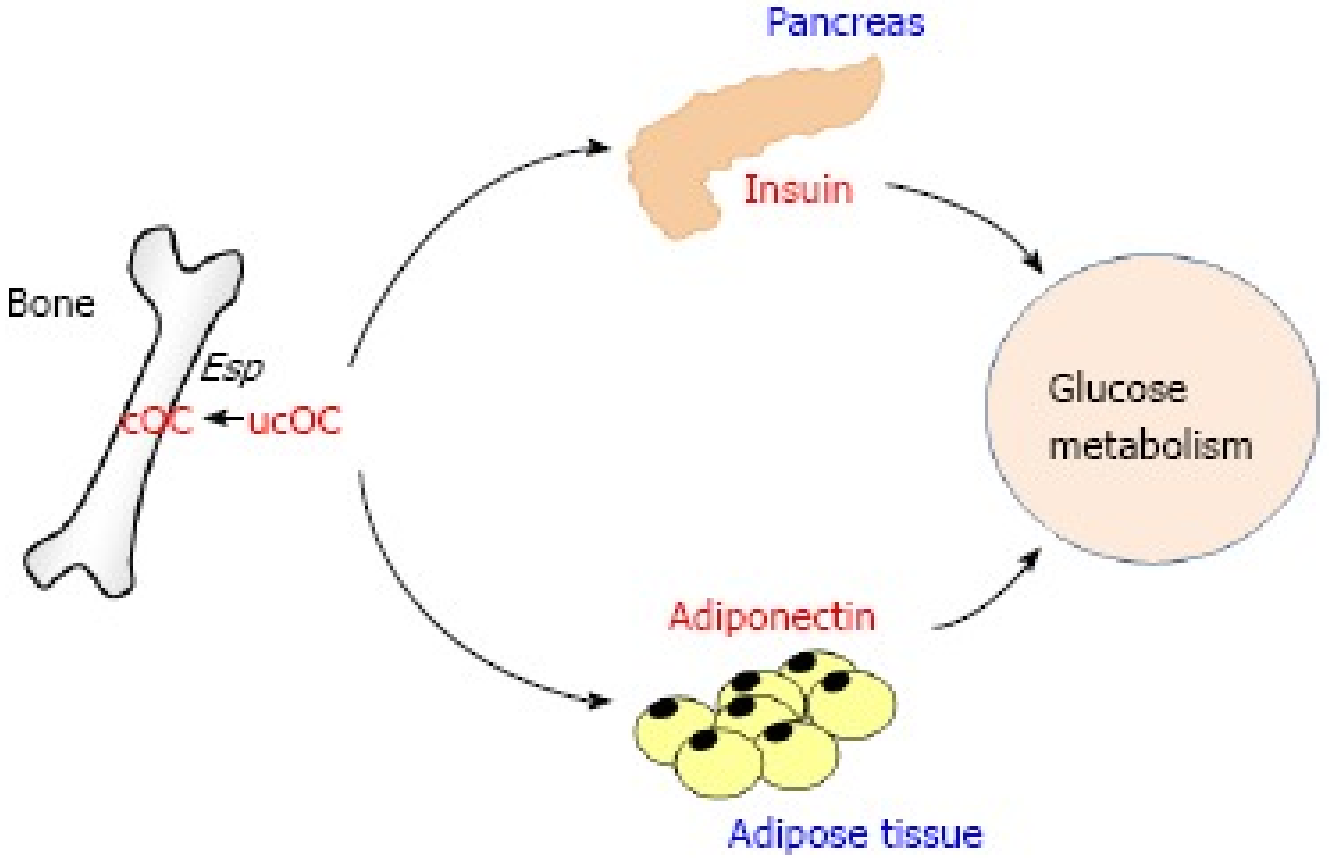
- The ASR stimulates osteocalcin release from bone within minutes
- Glutamate uptake into osteoblasts is required for osteocalcin release during an ASR
- Osteocalcin inhibits the parasympathetic tone during an ASR
- In adrenal insufficiency, increased osteocalcin levels enable an ASR to occur

Osteocalcin permits manifestations of the ASR to unfold by signaling in post-synaptic parasympathetic neurons to inhibit their activity, thereby leaving the sympathetic tone unopposed.

As long as glutamate uptake is present, a stress response can be mounted with the release of osteocalcin and **without any adrenal participation**.

Another function regulated by bone through osteocalcin is glucose homeostasis.

“Accumulating evidence has shown that osteocalcin, which is specifically expressed in osteoblasts and secreted into the circulation, regulates glucose homeostasis by stimulating insulin expression in pancreas and adiponectin expression in adipocytes, resulting in improving glucose intolerance. On the other hand, insulin and adiponectin stimulate osteocalcin expression in osteoblasts, suggesting that positive feedforward loops exist among bone, pancreas, and adipose tissue. In addition, recent studies have shown that osteocalcin enhances insulin sensitivity and the differentiation in muscle, while secreted factors from muscle, myokines, regulate bone metabolism. ***These findings suggest that bone metabolism and glucose metabolism are associated with each other through the action of osteocalcin****.”*


Pancreas
Insuin
Bone
Esp
cOC
ucOC
Glucose
metabolism
Adiponectin
Adipose tissue

“In addition to the direct effect of osteocalcin on insulin secretion, it has been shown that osteocalcin **indirectly** stimulates insulin secretion through increasing the secretion of glucagon-like peptide-1 (GLP-1), an incretin released by intestinal endocrine cells.”

Incretins involved: GLP-1 and GIP

“GLP-1 and GIP promote insulin secretion from pancreatic β-cells by inducing intracellular signals such as Ca2+ and cAMP. Metformin primarily acts by inhibiting glucogenesis in the liver and promoting glucose metabolism in the muscle. It is used as a concomitant drug with the incretin in the treatment of T2D.”

Chronic inflammation is linked to reduced GLP-1 production.

Glycolysis – first cellular step of glucose breakdown to use to for fuel.

Gluconeogenesis – formation of glucose from non-carbohydrate forms.

Glycogenolysis - release the stored glycogen in the form of usable glucose units from the liver and muscles to the bloodstream.

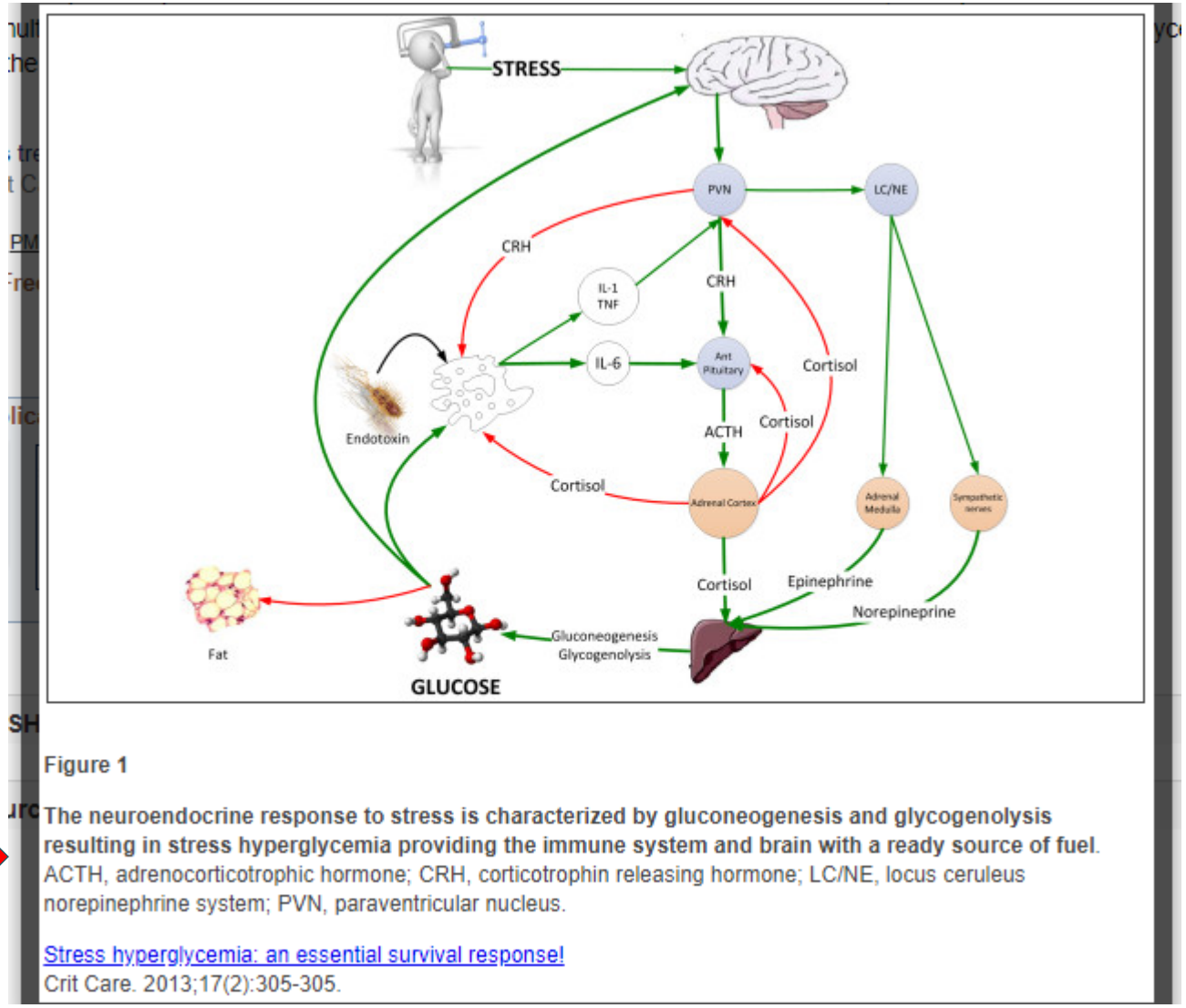
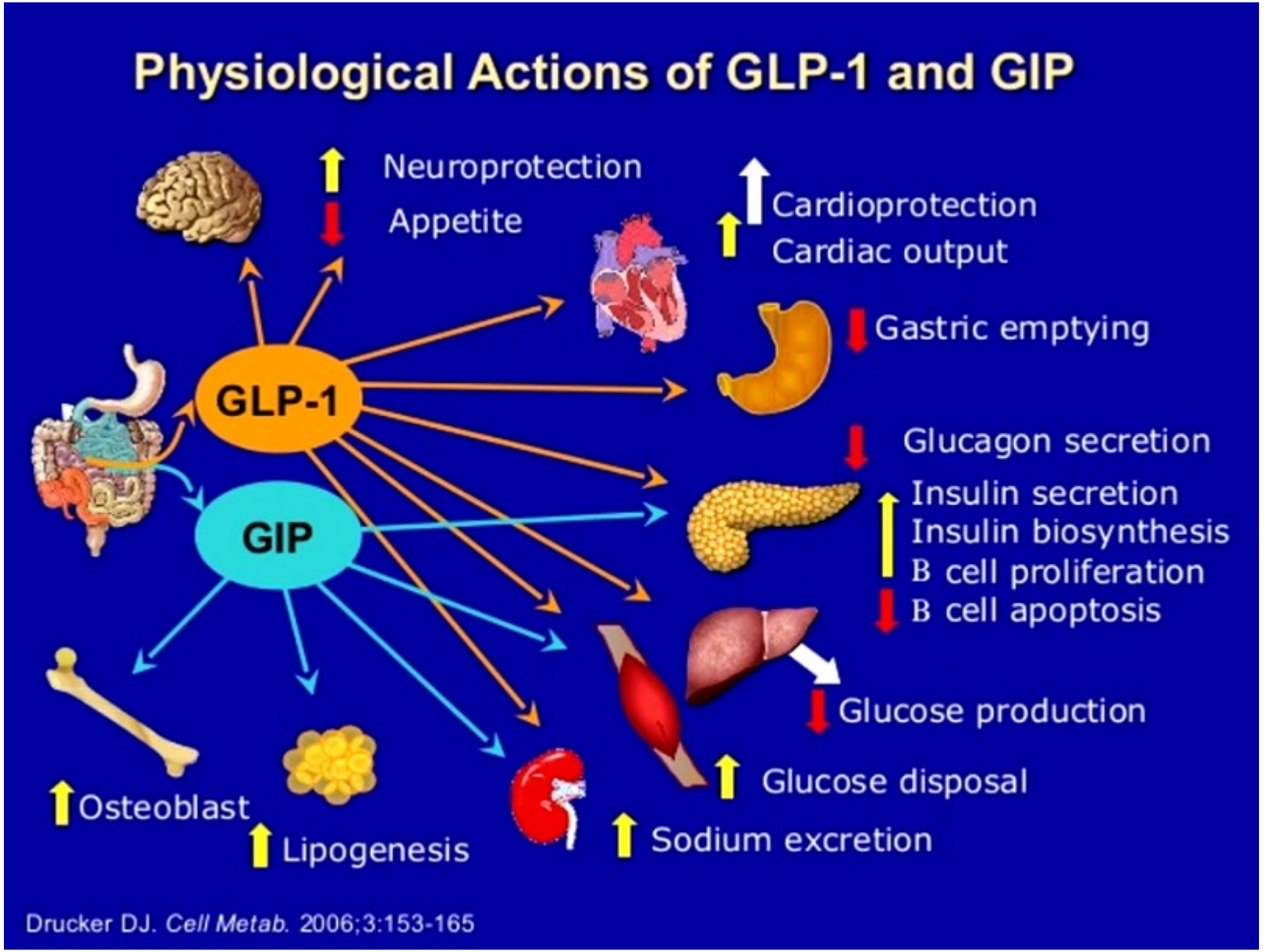


Figure 1

The neuroendocrine response to stress is characterized by gluconeogenesis and glycogenolysis resulting in stress hyperglycemia providing the immune system and brain with a ready source of fuel. ACTH, adrenocorticotrophic hormone; CRH, corticotrophin releasing hormone; LC/NE, locus ceruleus norepinephrine system; PVN, paraventricular nucleus.

Stress hyperglycemia: an essential survival response!
Crit Care. 2013;17(2):305-305.


Physiological Actions of GLP-1 and GIP
Neuroprotection
Appetite
Cardioprotection
Cardiac output
Gastric emptying
GLP-1
GIP
Glucagon secretion
Insulin secretion
Insulin biosynthesis
B cell proliferation
B cell apoptosis
Glucose production
Glucose disposal
Sodium excretion
Osteoblast
Lipogenesis
Drucker DJ. Cell Metab. 2006;3:153-165

*"**Stress hyperglycemia** is common in critically ill patients and appears to be a marker of disease severity. Furthermore, both the admission as well as the mean glucose level during the hospital stay is strongly associated with patient outcomes. Clinicians, researchers and policy makers have assumed this association to be causal with the widespread adoption of protocols and programs for tight in-hospital glycemic control. However, a critical appraisal of the literature has demonstrated that attempts at tight glycemic control in both ICU and non-ICU patients do not improve health care outcomes. **We suggest that hyperglycemia and insulin resistance in the setting of acute illness is an evolutionarily preserved adaptive responsive that increases the host's chances of survival. Furthermore, attempts to interfere with this exceedingly complex multi-system adaptive response may be harmful.** This paper reviews the pathophysiology of stress hyperglycemia and insulin resistance and the protective role of stress hyperglycemia during acute illness."*

Increase GLP-1 - suppress glycolysis, stops liver from pumping out glucose especially with too much post prandial glucose.