Casual Friday Presents

Patients on Medication Pt I
Metformin

A BIOGENETIX CLINICAL PRESENTATION

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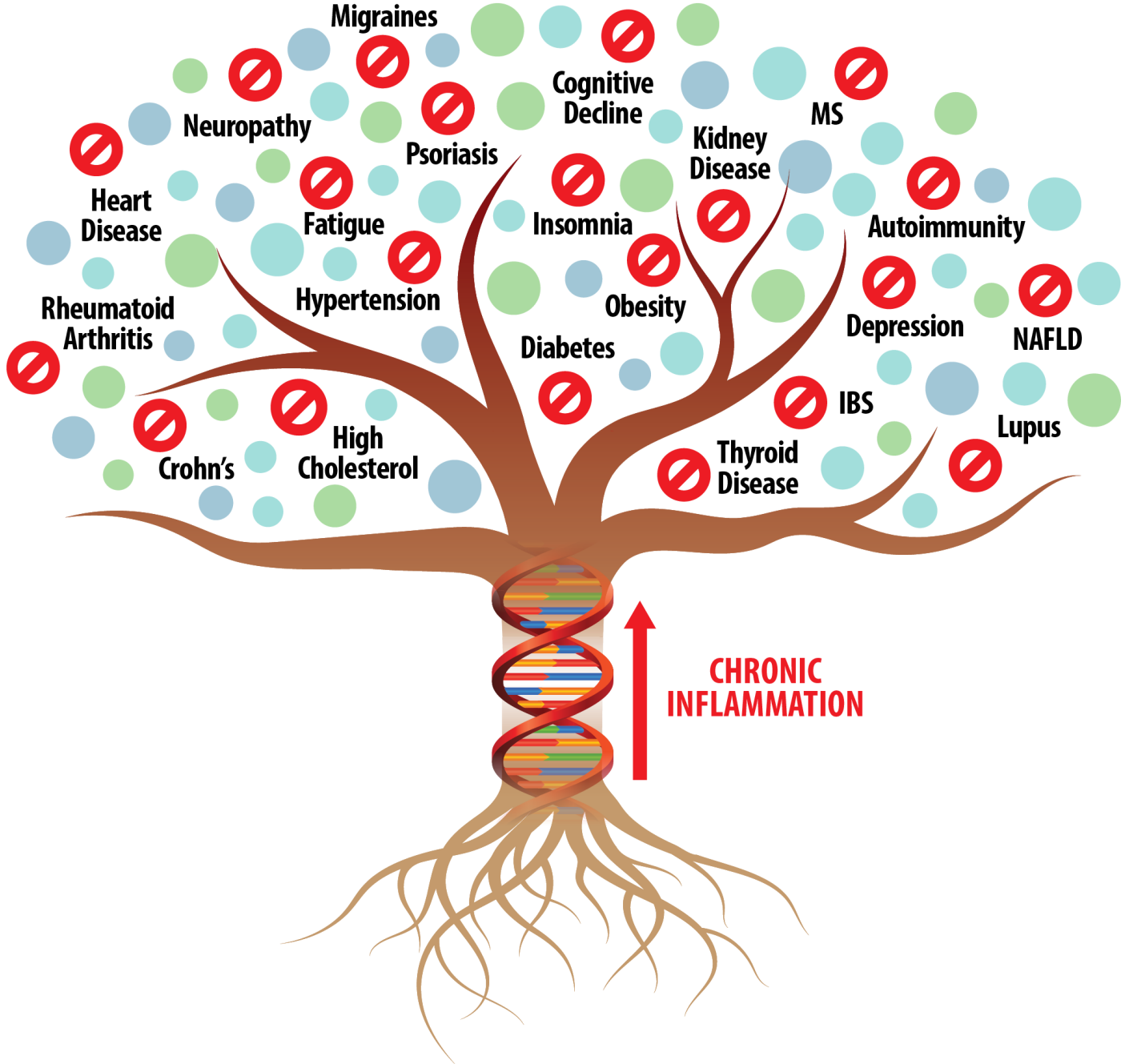
Migraines
Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Autoimmunity
Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Crohn's
High Cholesterol
Lupus
Thyroid Disease
CHRONIC INFLAMMATION

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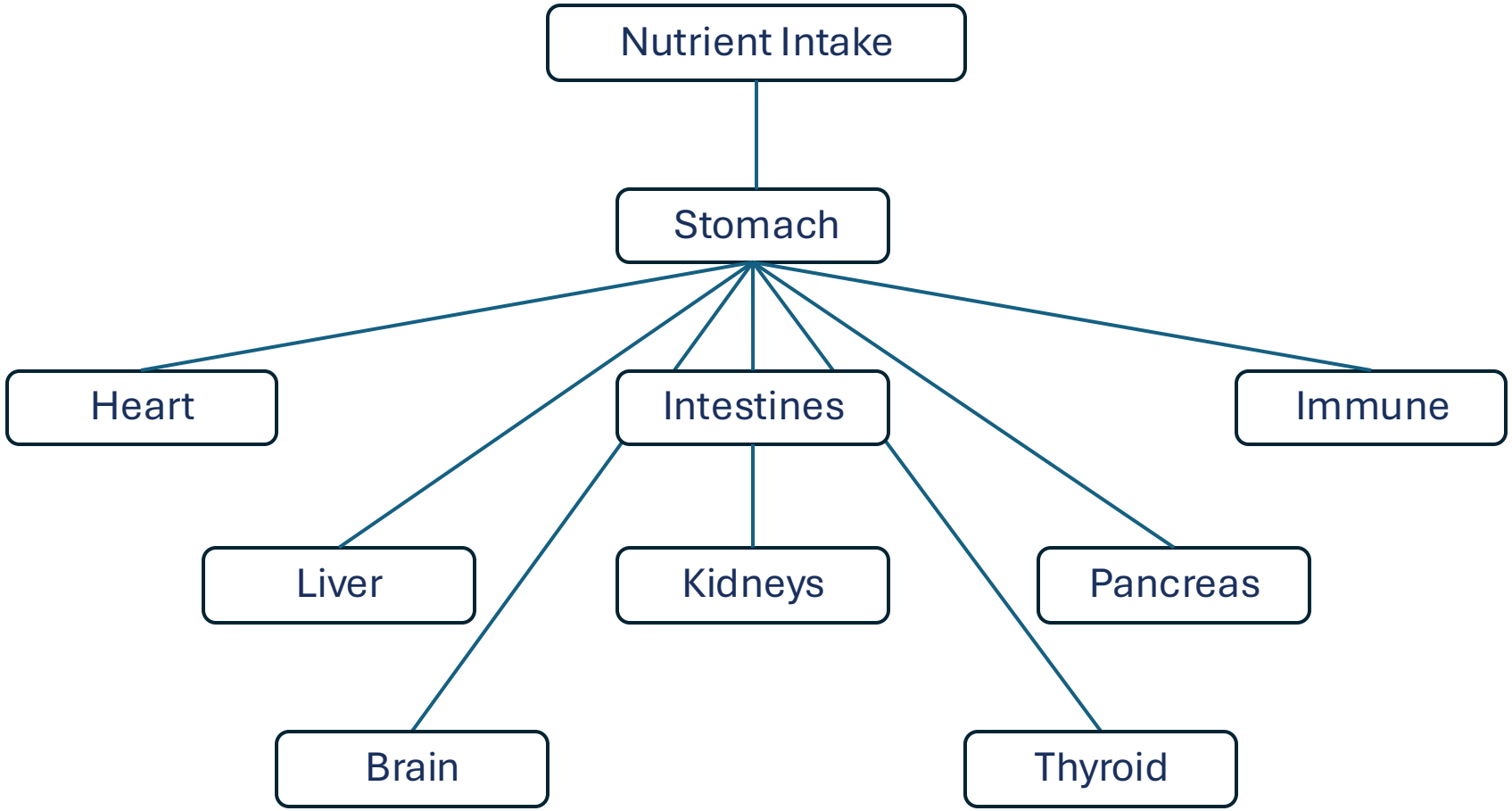
Nutrient Intake
Stomach
Heart
Intestines
Immune
Liver
Kidneys
Pancreas
Brain
Thyroid

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Report

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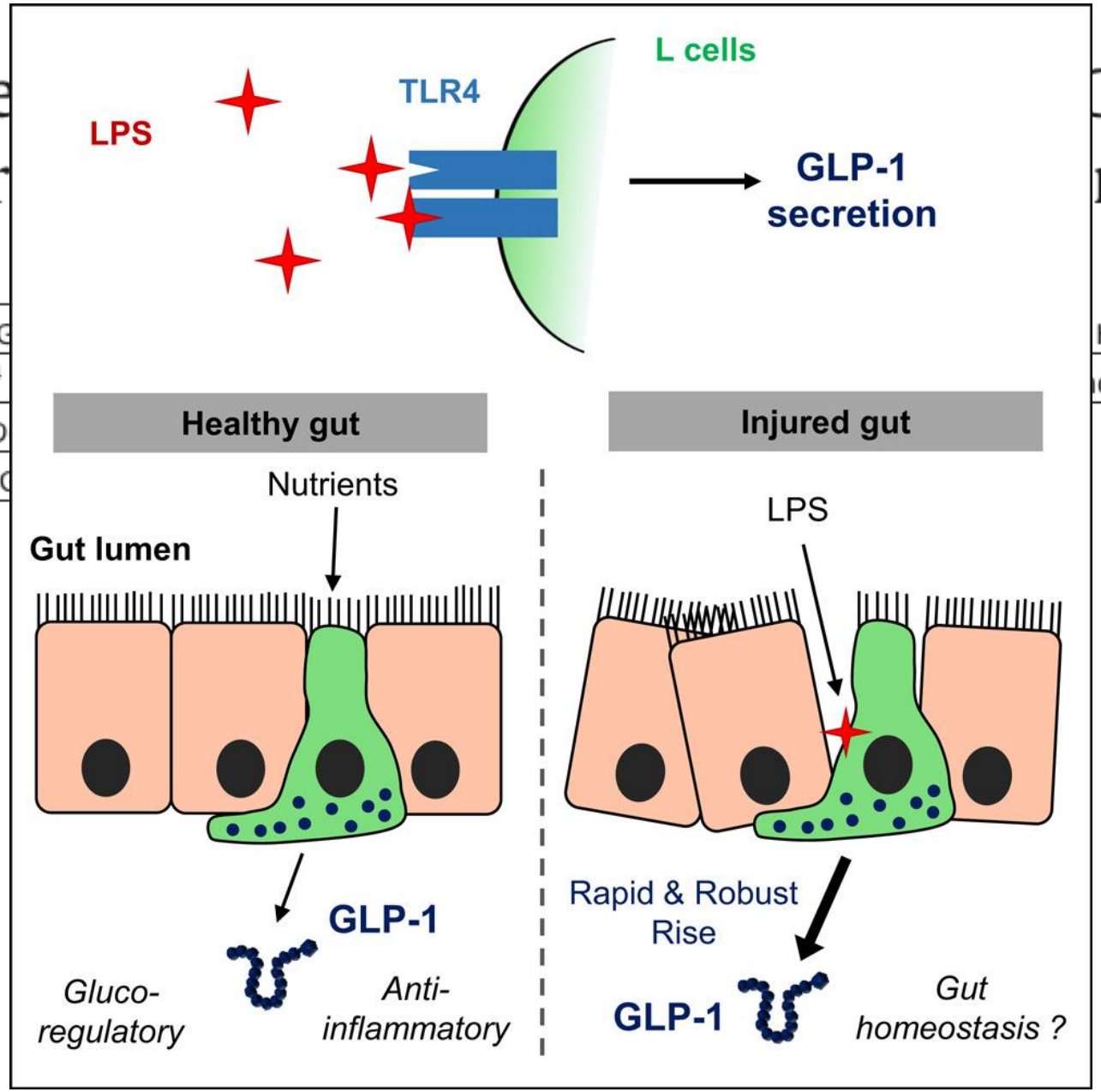

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Two Incretins to discuss:

1. GLP-1: Glucagon Like Peptide-1

2. GIP: Glucose – dependent Insulinotropic Polypeptide

Two Major Relationships to discuss:

1. **Glucose/Insulin**
2. **Liver/Glucagon**

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GLP-1 and Glucose Balance

GLP-1 (glucagon-like peptide-1) is an incretin hormone secreted from **intestinal L-cells** in response to nutrient intake. Its major physiological effects:

Effects
- **Enhances glucose-dependent insulin secretion**
- **Suppresses glucagon secretion** (when glucose is elevated)
- **Slows gastric emptying** (reducing postprandial glucose rise)
- **Promotes satiety**

Net effect:
➡ **Reduces hepatic glucose output** and **lowers postprandial glucose**.

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The two major incretins:

Feature	**GLP-1**	**GIP**
Secreted from	L-cells (distal gut)	K-cells (proximal gut)
Insulin secretion	Strong, glucose-dependent	Strong but “impaired” in T2D
Glucagon effect	↓ glucagon (in hyperglycemia)	↑ glucagon (in hypoglycemia & fasting)
Gastric emptying	Slows	Minimal
Appetite effect	↓ appetite	Marginal.

The Net Effect:

GLP-1 creates a **glucose-lowering hormonal environment**, while GIP is more of a **bidirectional amplifier** (insulin when high glucose; glucagon when low glucose).

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Incretins and Glucagon

GLP-1's effect on α-cells (glucagon)

•In **hyperglycemia**: GLP-1 → **suppresses glucagon release**
→ decreases liver gluconeogenesis & glycogenolysis

•In **WNL / hypoglycemia**: GLP-1 does **not** significantly suppress glucagon
→ prevents dangerous hypoglycemia

•GIP **enhances glucagon secretion** even postprandially, though less so during hyperglycemia.

•GLP-1's glucagon-lowering effect often predominates in hyperglycemia.

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GLP-1 and Liver Gluconeogenesis

GLP-1 **indirectly** regulates the liver.

Mechanisms of GLP-1 reducing hepatic glucose output
1.↓ Glucagon → ↓ cAMP → ↓ gluconeogenesis and glycogenolysis
(Primary mechanism)
2.↑ Insulin → ↑ hepatic glucose uptake & storage
3.Slower gastric emptying → ↓ substrate flux
4.Improved β-cell function → better postprandial insulin/glucagon ratio

Net effect:
➡ **Decreased gluconeogenesis**
➡ **Decreased hepatic glucose production**
➡ **Lower fasting and postprandial glucose**

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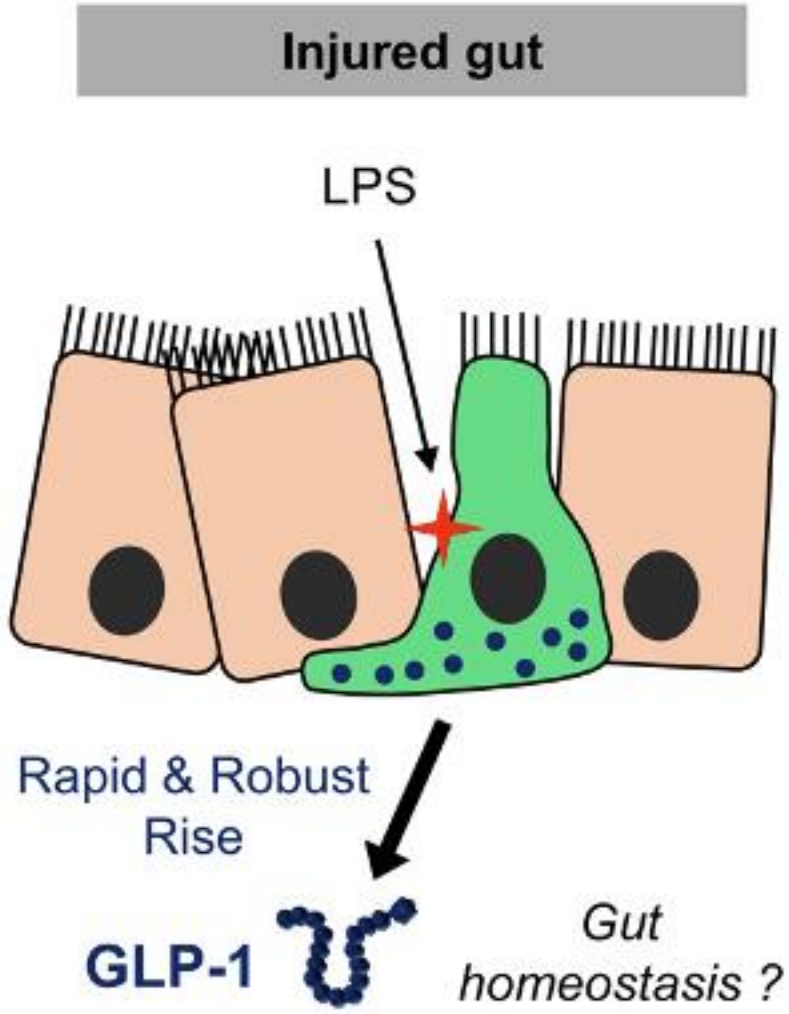
But what is the initial problem?



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Leading to:

Insulin Resistance at the alpha cells of the pancreas itself.

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When alpha cells won’t listen:

Mechanism	Effect
Impaired insulin signaling in alpha cells	Glucagon stays high
Impaired insulin signaling in liver	Liver ignores insulin’s suppression of glucose output
Elevated free fatty acids (lipotoxicity)	Stimulate glucagon secretion
Impaired incretin response (GLP-1, GIP)	Reduced suppression of glucagon after meals

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pharma intervention.

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Diabetologia. 2017 Aug 3;60(9):1577–1585. doi: 10.1007/s00125-017-4342-z

The mechanisms of action of metformin

Graham Rena [1], D Grahame Hardie [2,✉], Ewan R Pearson [1,✉]

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PMCID: PI

Given that gluconeogenesis is an energy-intensive process (consuming six ATP equivalents per molecule of glucose synthesised), hepatocytes need to balance the demand for ATP with supply, with the latter primarily provided by mitochondria. Metformin accumulates within mitochondria to concentrations up to 1000-fold higher than in the extracellular medium, because metformin carries a positive charge and the membrane potentials across the plasma membrane and mitochondrial inner membrane (positive outside) drive metformin into the cell and subsequently into the mitochondria (Fig. 2) [14, 15]. The most intensively studied mitochondrial action of metformin is the inhibition of Complex I of the respiratory chain [14, 16], which suppresses ATP production. A persistent criticism of this mechanism has been the high extracellular concentrations (mmol/l) required to observe rapid effects, although lower concentrations of metformin (50–100 μmol/l) do inhibit Complex I in rat hepatoma (H4IIE) cells after several hours; this delay was ascribed to the slow uptake of metformin by mitochondria [14], which has recently been observed experimentally [15]. In addition, some studies do not detect any changes in cellular ADP:ATP ratios after metformin treatment, although they can be observed with phenformin [17]. In cells carrying out gluconeogenesis, concomitant suppression of this pathway [18] might explain modest effects on ADP:ATP ratios. Other consequences of respiratory chain inhibition besides ATP production, such as changes in the NAD^+:NADH ratio, may also contribute to the effects of metformin on gluconeogenesis [16].

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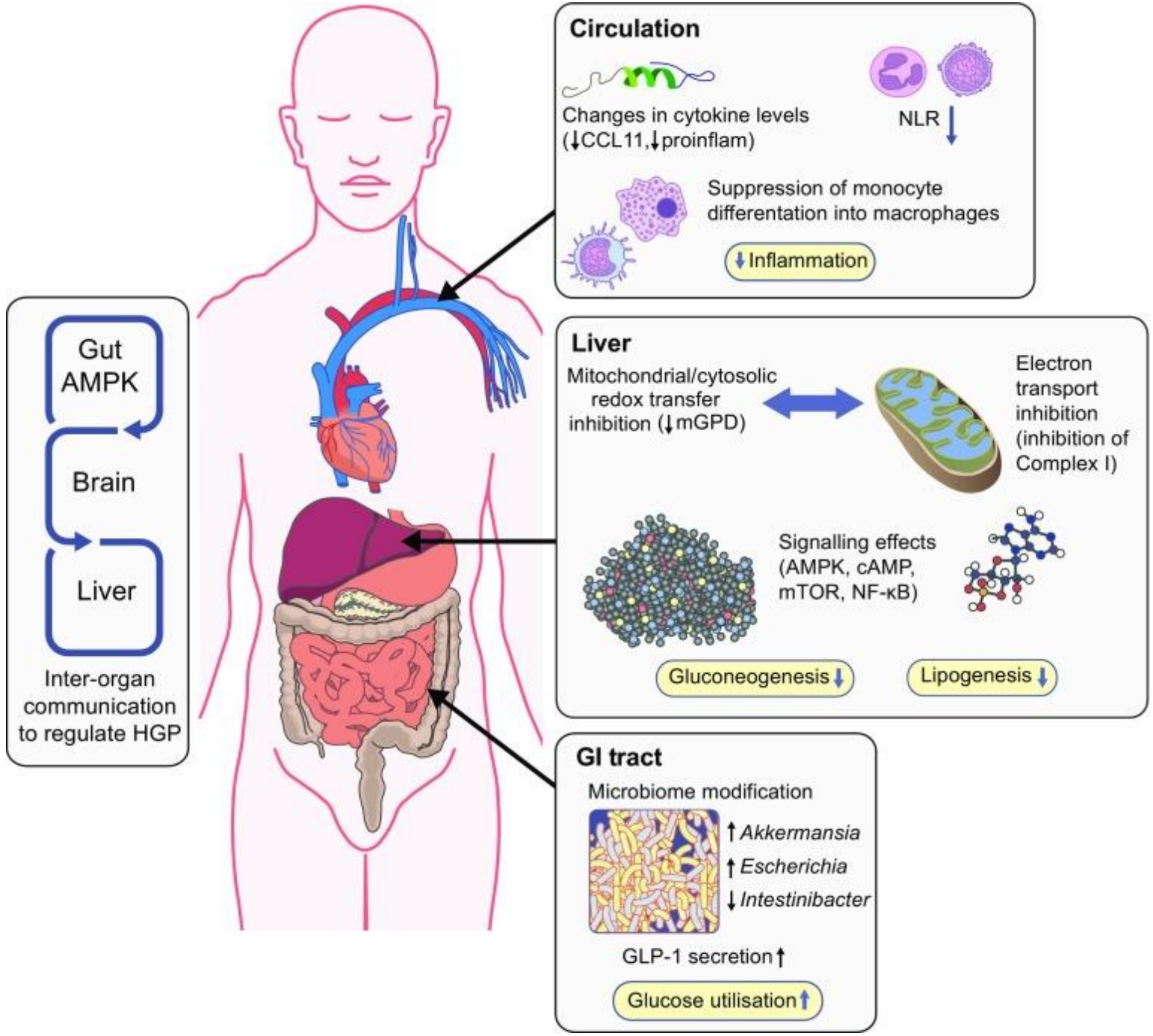
Inhibition of mitochondrial function can also explain metformin's ability to activate the cellular energy sensor AMP-activated protein kinase (AMPK). Once activated by increases in AMP:ATP and ADP:ATP ratios (indicative of cellular energy balance being compromised), AMPK acts to restore energy homeostasis by switching on catabolic pathways generating ATP, while switching off cellular processes consuming ATP (Fig. 2) [24, 25]. Since it causes a switch from synthesis of cellular nutrient stores to their breakdown, the idea that AMPK might be involved in metformin action was attractive and, in 2001, metformin was reported to activate AMPK in rat hepatocytes and rat liver in vivo [26]. Although high concentrations (500 µmol/l) of metformin were required to observe AMPK activation after brief (1 h) treatment of cells, significant effects were observed after incubation for much longer periods with just 20 µmol/l metformin, more compatible with concentrations of the drug found in the portal vein. Supporting the idea that biguanides acted by increasing cellular AMP:ATP/ADP:ATP ratios, AMPK was not activated by either metformin or phenformin in cells expressing an AMPK mutant that is insensitive to changes in AMP or ADP [17]. However, AMPK can also be activated by glucose starvation, and by low concentrations of metformin, by a different mechanism involving the formation of a complex with the proteins Axin and late endosomal/lysosomal adaptor, MAPK and mTOR activator 1 (LAMTOR1; Fig. 2), the latter being a lysosomal protein [27]. Thus, metformin might also activate AMPK by a mechanism involving the lysosome, rather than the mitochondrion.



https://pmc.ncbi.nlm.nih.gov/articles/PMC5552828/

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The mechanisms of action of metformin

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PMCID: PMC5552828 PMID: 28776086

Physiologically, metformin acts directly or indirectly on the liver to lower glucose production, and acts on the gut to increase glucose utilisation, increase GLP-1 and alter the microbiome. At the molecular level, metformin inhibits the mitochondrial respiratory chain in the liver, leading to activation of AMPK, enhancing insulin sensitivity (via effects on fat metabolism) and lowering cAMP, thus reducing the expression of gluconeogenic enzymes. Metformin also has AMPK-independent effects on the liver that may include inhibition of fructose-1,6-bisphosphatase by AMP. As cell and tissue responses are not only a product of dose, but also of treatment duration and model used, we suggest that the physiological relevance of the effects of metformin identified in cells is best validated through studies carried out in vivo, ideally in humans given metformin by the oral route.

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Metformin Action In Short:

- enter hepatocytes and slow down how much energy they make
- flipping on AMPK, the “low energy” protector
- stopping the liver from making new sugar
- reducing fat in the liver
- blocking glucagon signals that normally tell the liver to pump out glucose

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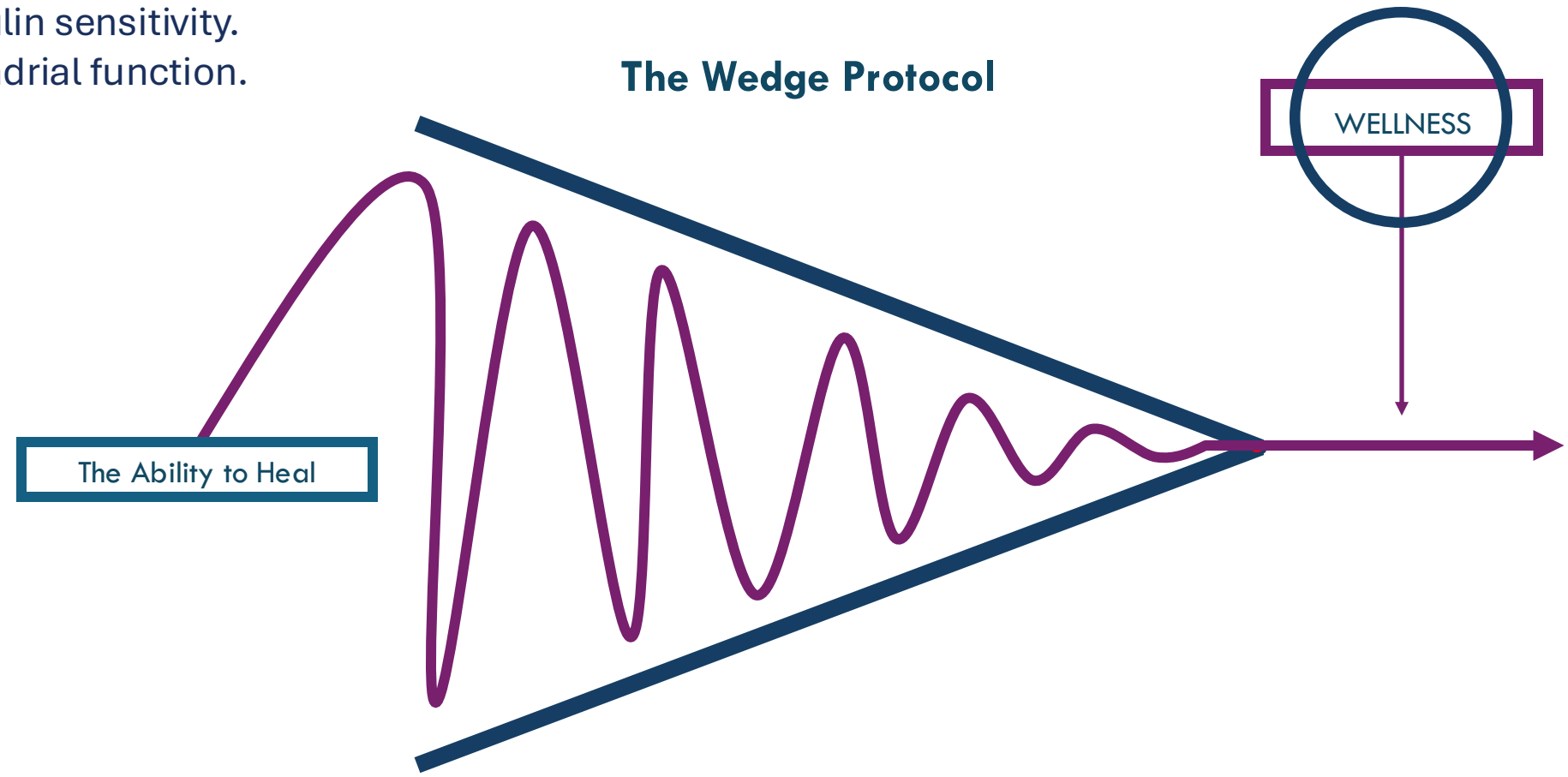
The Strat:

1. Slow enteroendocrine injury.
2. Decrease systemic inflammatory drivers.
3. Support ideal insulin sensitivity.
4. Support mitochondrial function.



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