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Galangin inhibits glucose-induced insulin secretion through the alteration of mitochondrial oxidative phosphorylation

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Introduction
Glucose stimulates insulin secretion through a complex metabolic sequence that includes mitochondrial respiration, ATP synthesis, Kₐ₉ channels closing, calcium entry via L-type calcium channel (Cav) activation and exocytosis. We and others previously reported that flavonoids regulate glucose-induced insulin secretion by targeting key signaling proteins and cellular processes. Here, we examined the pharmacological behavior of the flavonoid galangin on insulin secretion and we investigated its mechanism of action by focusing on mitochondrial function.

Methods
INS-1 β-cells or rat isolated pancreatic islets were incubated for 60 min in Krebs-Ringer bicarbonate buffer with or without glucose, flavonoid and secretagogues. Insulin release was quantified by the homogeneous time-resolved fluorescence (HTRF) method (Cisbio). Intact INS-1 β-cells oxygen consumption was measured using the high-resolution Oxygraph-2k (OROBOROS instruments). Results are presented as mean ± SEM and were analyzed by one-way or two-way ANOVA and Holm-Sidak’s multiple comparisons test. n = 5.

Figure 1. Chemical structure of galangin.

Figure 2. Galangin inhibits glucose induced insulin secretion. Under glucose stimulant condition (8.3 mM), galangin inhibits insulin secretion for concentrations equal to and greater than 20 μM in INS-1 β-cells (A) and in rat isolated pancreatic islets (B). In both models, galangin has no effect in basal condition (1.4 or 2.8 mM glucose).

Figure 3. Multiple secretagogues are used to stimulate islet cells and increase insulin secretion. Insulin release was quantified by the homogeneous time-resolved fluorescence (HTRF) method (Cisbio). Intact INS-1 β-cells oxygen consumption was measured using the high-resolution Oxygraph-2k (OROBOROS instruments). Results are presented as mean ± SEM and were analyzed by one-way or two-way ANOVA and Holm-Sidak’s multiple comparisons test. n = 5.

Figure 4. Galangin differently inhibits insulin secretion depending of secretagogues tested in INS-1 β-cells. Galangin (20 μM) strongly inhibits insulin secretion induced by three substrates of mitochondrial metabolism: leucine (5 mM), pyruvate (5 mM) and methylsuccinate (5 mM). In contrast, galangin has no effect on insulin secretion induced by the Kₐ₉ inhibitor glibenclamide (10 nM).

Figure 5. Galangin modulates mitochondrial oxygen consumption in INS-1 β-cells. Exploration of mitochondrial oxidative phosphorylation (OXPHOS) chain with inhibitors (rotenone, antimycin and oligomycin) and uncoupler (CCCP) (A). Galangin (20 μM) increases basal (routine), proton leak-associated (leak) and maximal electron transport system (ETS) respiratory rates (R₂, R₃). O₂ flux control ratio (ratio of oxygen consumption dedicated to ATP synthesis and proton leak over routine respiration) reaches 60 % for mitochondrial ATP synthesis and 40 % for proton leak in control condition (DMSO). Galangin reverts this ratio, with only 40 % of O₂ consumption dedicated to ATP synthesis and 60 % to proton leak (D).

Figure 6. CCCP inhibits glucose-induced insulin secretion in INS-1 β-cells. Under glucose stimulant condition (8.3 mM), CCCP inhibits insulin secretion in a concentration dependent manner. Inhibition induced by 0.4 μM CCCP is equivalent to that observed with galangin 20 μM.

Conclusion
Our work suggests that galangin inhibits glucose-induced insulin secretion by altering mitochondrial respiration. Indeed galangin inhibits the effect of secretagogues which need mitochondrial activity to induce insulin secretion, but has no effect on secretagogue which induce insulin secretion independently of mitochondria. Galangin behaves like the mitochondrial OXPHOS uncoupler CCCP and decreases the part of oxygen consumption dedicated to ATP synthesis. Therefore, we are currently investigating whether galangin impairs mitochondrial glucose-stimulated ATP synthesis.