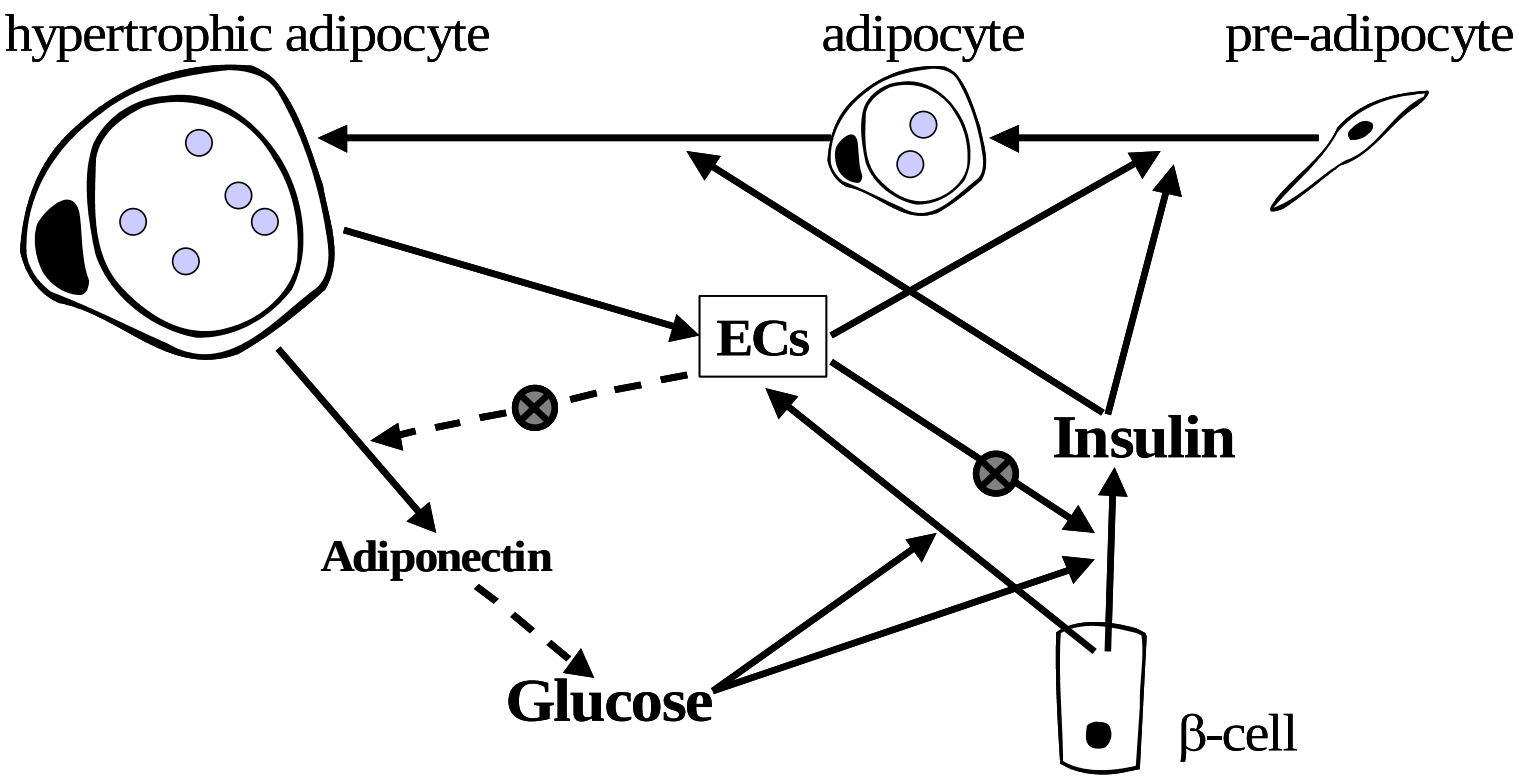
Supplemental Figure 1. **Adipocyte-β-cell communication in obesity and hyperglycaemia: possible disruption by the endocannabinoids**

According to the experiments carried out in the present study with models of adipocytes and β-cells, high serum glucose levels cause endocannabinoid (EC) release from β cells. Under conditions of obesity and pre-diabetes, insulin, instead of inhibiting glucose-induced EC elevation, stimulates EC levels *per se*. The subsequent up-regulation of EC levels causes, via CB_1 receptors, further release of insulin from β cells. A vicious circle is therefore established in β cells whereby ever increasing EC and insulin amounts are produced from these cells. Excess insulin and EC accelerate adipocyte differentiation and causes the formation of hypertrophic adipocytes, which carry on producing ECs. Excess ECs from both β-cells and adipocytes inhibit, via CB_1 receptors, adiponectin expression while keeping on stimulating insulin release and, through these two actions, contribute to reduce insulin sensitivity and increase hyperglycaemia, thereby establishing another vicious circle including hypertrophic adipocytes, β-cells and other insulin-sensitive and glucose-utilizing cells. Blockade of CB_1 receptors, by increasing adiponectin production and inhibiting EC-induced insulin release from β-cells, interrupts these vicious circles, thereby causing beneficial effects that are independent from body weight loss.

Broken arrows denote inhibition, full arrows denote activation. Crossed circles denote processes that are blocked by CB_1 receptor antagonists


hypertrophic adipocyte
adipocyte
pre-adipocyte
ECs
Insulin
Adiponectin
Glucose
β-cell