**Dapagliflozin modulates SGLT1 and GLUT2 expression and glucagon secretion in a SGLT2-independent manner in murine alpha cells**

A. Solini¹, L. Nigi², E. Santini¹, G. Sebastiani², B. Astiarraga¹, C. Rossi¹, F. Dotta²;
¹Dept of Clinical and Experimental Medicine, University of Pisa, ²Department of Medicine, Surgery and Neuroscience, University of Siena, Italy.

**Background and aims:** SGLT2 inhibitors reduce plasma glucose levels via a forced glycosuria through inhibition of glucose uptake by the kidney, with a fully insulin-independent mechanism. However, recent studies show increased glucagon concentrations after acute or chronic administration of SGLT2 inhibitors. Whether or not such effect is consequence of a series of systemic metabolic variations rather than due to a direct effect on pancreatic α-cells is unclear.

**Materials and methods:** We tested this hypothesis by treating for different times (30, 45, 60 min and 12 h) murine pancreatic α-cell line (alpha-TC1) with 100 ng/ml dapagliflozin (Dapa), and measuring its effect on the expression of glucose transporters, molecular mediators of hormone secretion and glucagon and GLP-1 release.

**Results:** SGLT2 was not detectable in these cells even by digital PCR technique. SGLT1, was quite abundantly represented and was significantly increased by Dapa at 30’ and 45’ (+65±21% and + 16±3% vs untreated, p<0.001 and 0.05, respectively). GLUT1 expression was substantially unaffected by Dapa (-5% at 30’and -7% at 45’), while GLUT2 was down-regulated (-24±60% at 30’ and -19±23% at 45’, both p<0.005). At 12 h, the expression of both glucose transporters returned to baseline levels. Similarly, Dapa did not induce variations in the expression of several molecules involved in the modulation of glucagon release or α-cell phenotype (fold induction at Dapa 30’ vs untreated= CHGA: 1.10±0.17; PAX6 1.13±0.1; PCSK2: 1.20±0.18; PCSK1: 0.99±0.18; SYP: 1.14±0.23, all p=ns). Moreover, GLP-1 receptor expression did not differ in α-cells treated or untreated with Dapa. Accordingly, glucagon release minimally changed in cells pretreated with Dapa (at 30’: 822±76 vs 828±85; at 45’: 1198±127 vs 1515±112pg/ml/µg protein, both p=ns). Of note, at 12 h, glucagon release was significantly lower in Dapa-treated cells (3524±254 vs 2446±157pg/ml/µg protein, p< 0.005). GLP-1 did not significantly change after Dapa (at 30’: 822±76 vs 828±85; at 45’: 1198±127 vs 1515±112pg/ml/µg protein, both p=ns). At 12 h, GLP-1 was 353±216 in untreated cells and 3604±270pmol/ml/µg in Dapa-treated cells (p=ns). Low (5.5 mM) or high (25 mM) glucose pulses did not affect SGLT1, GLUT1 or GLUT2 expression, while glucagon (2210±125 vs 1725±117pg/ml/µg protein, p<0.05) and GLP-1 release (2671±139 vs 2090±154pmol/ml/µg protein, p<0.01) secretion were slightly but significantly reduced by high glucose.

**Conclusion:** Dapa acutely upregulates SGLT1 and downregulates GLUT2 expression in pancreatic α-cells, while SGLT2 was not detectable in these cells. In addition, glucagon release was significantly reduced after long-term (12h) treatment with Dapa. These data suggest that the glucagon raise reported in type 2 diabetes patients treated with Dapa does not reflect the direct action of this molecule on pancreatic α-cells.

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