Diabetes is associated with decreased pancreatic β-cell function and mass. It is unclear whether diabetes treatment should aim at restoring β-cell performance/mass or at inducing “β-cell rest” to prevent further deterioration. The transcription factor Foxo1 protects β-cells against oxidative stress induced by hyperglycemia and prevents β-cell replication in insulin-resistant states. Here we show that these combined effects are associated with a concerted repression of genes involved in glycolysis, nitric-oxide synthesis, G protein-coupled receptor signaling, and ion transport. Conversely, Foxo1 increases expression of several neurotransmitter receptors and fails to regulate target genes predicted from Caenorhabditis elegans and Drosophila studies. Functional analyses show decreased glucose utilization and insulin secretion in β-cells overexpressing Foxo1. We propose the definition of “metabolic diapause” for the changes induced by Foxo1 to protect β-cells against oxidative stress. The data provide genetic underpinning for the concept of β-cell rest as a treatment goal in diabetes.

Type 2 diabetes is caused by a combination of insulin resistance and impaired β-cell function (1). Defects of β-cell function in diabetes are complex and include reduced insulin secretion and alterations of β-cell mass (2). Moreover, there are both genetic and acquired (environmental) components to β-cell failure. Thus, an impairment of glucose-stimulated insulin secretion can be detected in nondiabetic first degree relatives of diabetic patients, consistent with a genetic predisposition (3, 4). However, following the onset of diabetes, hyperglycemia itself causes a deterioration of insulin secretion, which can be partly reversed by improved glycemic control (5), demonstrating a role of acquired metabolic abnormalities in β-cell failure (6). Indeed, an apparently inexorable decline of β-cell function is a hallmark of diabetes and a major cause of therapeutic failure (7).

Agents that reverse or prevent β-cell failure play an important role in diabetes treatment, and two new classes of drugs that target β-cells have been recently introduced as adjuvant treatments for diabetes (8). There persists, however, a fundamental ambiguity about the goal of therapies targeting the β-cell. Simply put, the question is whether the goal should be to preserve β-cell function by reducing the metabolic demand on the β-cell (“β-cell rest”) (9–13) or to increase β-cell performance in the face of high metabolic demand (14).

It remains unclear whether the two primary components of β-cell failure, impaired insulin secretion and reduced β-cell mass (15), are mechanistically linked. Turnover studies in mice support the view that β-cells are capable of a limited number of replications (16), suggesting that the decrease of β-cell mass in humans with diabetes is the result of an exhaustion of the proliferative capacity of the β-cell. Thus, understanding the mechanism linking β-cell renewal and insulin secretion can provide clues to the best therapeutic approach to β-cell failure.

The forkhead transcription factor Foxo1 regulates β-cell proliferation in insulin-resistant states (17, 18) and promotes a state of “premature senescence” (19–21) to protect β-cells against hyperglycemia-induced oxidative stress (22). In addition, Foxo1 activity in β-cells is modulated by GLP-1 (23), glucose (24), and oleic acid (25). Thus, Foxo1 represents a potential relay node to integrate β-cell function in response to nutrients and hormones with β-cell turnover. To understand the mechanism by which Foxo1 controls these processes, we determined the RNA expression profile of cultured β-cells with a gain of function in Foxo1.

**EXPERIMENTAL PROCEDURES**

**Reagents and Cell Culture**—Cell culture reagents were from Invitrogen, 5-3H- and U-14C-labeled glucose were from American Biosciences, and anti-Foxo1 antiserum was from Cell Signaling (Beverly, MA). Clone 832/13 derived from INS1 cells (26) (passages 46–70) was expanded and grown in monolayer cultures (27). Western blot was performed according to standard procedures on proteins isolated during RNA extraction (28). Protein concentrations were determined using the Pierce BCA protein assay.

**Recombinant Adenovirus Transduction**—The mutant Foxo1 carries single amino acid substitutions replacing the three main phosphorylation sites, Thr324 → Ala, Ser253 → Asp, and Ser316 → Ala, and has been described previously (29). INS832/13 cells were seeded 2 days before use and transduced with adenovirus encoding Foxo1 or β-galactosidase at a multiplicity of infection of 50 plaque-forming units/cell for 1 h in 1 ml of complete medium. The adenoviral solution was replaced with complete medium, and cells were
allowed to recover for 24 h before the experiment. Under these conditions, >95% of the cells are transduced (not shown).

Gene Expression—RNA was isolated with Trizol reagent (Invitrogen) from three independent experiments. Semiquantitative or quantitative real time PCRs (Opticon 2, MJ Research, Waltham, MA) were performed as described previously (30). Primer sequences are available upon request.

Cell Proliferation—INS832/13 cell proliferation was evaluated using a BrdUrd3 enzyme-linked immunoassay kit (Roche Applied Science). Adenovirus-transduced INS832/13 cells were seeded in 96-well plates (8 × 104 cells/well) and allowed to recover for 24 h. BrdUrd was added to the culture medium for 1 h, and cells were fixed, incubated with peroxidase-conjugated anti-BrdUrd antibody, and the immune complexes were quantified by enzyme-linked immunosorbent assay (Bio-Rad).

Cell Death and Apoptosis—Cells were plated in 6-well plates and cultured until 80% confluent. Following transduction with β-galactosidase or Foxo1 or treatment with 25 μM H2O2 for 1 h to induce apoptosis (31), we measured caspase-3 activation and cell toxicity using the CaspACE and CytoTox 96 cytotoxicity (Promega) assay systems, respectively. The CytoTox 96 assay measures the release of cytoplasmic enzymes in the medium upon loss of membrane integrity as a result of cytotoxicity. Simultaneously, cells were harvested to measure apoptosis. After a brief centrifugation at 450 × g, cell pellets were resuspended in lysis buffer, and caspase-3 activity was determined by adding assay buffer containing the DEVD-p-nitroanilide substrate.

Insulin Secretion and Total Insulin Content Assays—70% confluent INS832/13 cells were seeded in 24-well plates 1 day before use. On the day of the experiment, cells were washed and incubated for 30 min in 2.8 mM glucose KRBH buffer before incubation for 30 min at different glucose concentrations (2.8 and 16 mM) or 35 mM KCl to induce cell depolarization. At the end of the incubation, culture medium was collected, centrifuged to remove cells, and assayed for rat/human insulin content by radioimmunoassay (Linco, St. Charles, MO). Total insulin content was measured after acid ethanol extraction (32).

Glucose Metabolism—We measured glucose oxidation as 14CO2 production from [U-14C]glucose and glucose utilization by measuring 3H2O production from [5-3H]glucose (33). We carried out the two determinations simultaneously and terminated the reactions by the addition of 40% perchloric acid. Trifluoracetic acid was separated by chromatography on AG1X8 column (Bio-Rad). 14CO2 was captured by glass fiber filters previously soaked in 5% KOH.

Microarray Analysis—RNA was isolated from INS832/13 cells 24 h post-transduction using the Trizol reagent (Invitrogen) from four replicate samples. RNA samples were reverse-transcribed, labeled, and hybridized to a rat 230A DNA microarray (Affymetrix, Santa Clara, CA) according to the manufacturer’s instructions. The mean expression value of samples derived from cells overexpressing Foxo1 and β-galactosidase was compared for each set of probes. Of the 15,924 sets of probes represented on the microarray, 4725 were considered present in at least one of the two conditions according to the software threshold, and 2237 changed significantly upon CN-Foxo1 overexpression, using a false discovery rate of 5% to declare significance. Among these, we detected 721 known genes and 1516 expressed sequence tags. The full list of genes with an altered expression profile is shown in supplemental Table 1. Gene expression data were further analyzed with the ErmineJ bioinformatics tool. ErmineJ performs analyses of gene sets in expression microarray data to determine whether specific biological pathways are significantly altered. We used p = 0.05 as a threshold to declare significance.

Chromatin Immunoprecipitation—Chromatin immunoprecipitation assay kits (Upstate Biotechnology, Inc., Lake Placid, NY) were used as described (34). 106 INS823/13 cells were growth-arrested by serum deprivation overnight, fixed in 1% formaldehyde, washed, and resuspended in lysis buffer. Samples were sonicated to shear DNA to lengths of 200–1,000 bp, and the material was immunoprecipitated with anti-Foxo1 antibody (Santa Cruz Biotechnology, Inc., Santa Cruz, CA). DNA was recovered and amplified by PCR using oligonucleotides flanking the assayed promoter regions (34).

Statistical Analysis—Data are expressed as mean ± S.E. Statistical analysis was performed using analysis of variance and Student’s t test. We used p < 0.05 to declare statistically significant differences.

RESULTS

RNA Profiling of INS832/13 Cells Overexpressing Foxo1—We reasoned that, if Foxo1 protects β-cells against hyperglycemia, the transcriptional profile of β-cells expressing constitutively nuclear Foxo1 (Foxo1-ADA, bearing mutations of Akt phosphorylation sites) (22) should reveal the mechanism(s) of this protective effect. Since we previously showed that the Foxo1 response is identical in cultured β-cells and primary islets (22), in this study we used cultured β-cells (clone INS832/13) to allow for efficient adeno viral transduction. To minimize artifacts associated with gain-of-function of transcription factors, we used moderate overexpression and monitored its effects on cell survival and canonical Foxo1 target genes. Immunoblot analysis indicated that Foxo1 levels increased ~5-fold following Foxo1 transduction (Fig. 1A) and resulted in a ~6-fold increase of Ifgpb1 expression (Fig. 1B, Table 1), similar to previous reports (17, 35). Consistent with data in transgenic and knock-out mice indicating that Foxo1 controls β-cell proliferation (17, 18, 35), we detected a 50% decrease in BrdUrd incorporation into Foxo1-expressing cells (Fig. 1C).

We identified 721 genes, expression of which was altered by Foxo1 (supplemental Table 1). To validate the microarray data, we used quantitative PCR to investigate changes of selected Foxo targets in an independent set of experiments. These data confirm the extent of the changes observed in the microarray (Table 1). To sample Foxo1 occupancy of candidate forkhead sites in target promoters, we carried out chromatin immunoprecipitation assays. We detected Foxo1 at the Ifgpb1, Foxa2,
and Isl1 promoters (Fig. 2), consistent with the idea that these genes are direct targets of Foxo1.

**Foxo1 Inhibits Glycolysis and Reduces Glucose Competence**—Analysis of biochemical pathways affected by Foxo1 with the Erminej software indicated a concerted decrease in the expression of glycolytic genes (Table 2). Of note, we detected decreases of Pkg (10-fold), Pfkfb2, Chrebp (3-fold), Gck, and Slc2a2 (Glut2) (2-fold). The predicted outcome of these changes would be decreased glucose utilization and glucose-stimulated insulin secretion (Fig. 3A). In control cells, changes in glucose concentration from 2.8 to 16 mM resulted in a 3-fold increase of glucose oxidation (Fig. 3B). These data support the findings of the RNA profiling studies. Foxo1 transduction also induced a 65% decrease of glucose-dependent glucose utilization (Fig. 3C).

Because glucose metabolism is required for insulin release, we measured glucose-dependent insulin secretion. Consistent with the decrease in glucose utilization and oxidation, Foxo1 inhibited glucose-induced insulin secretion, whereas the control β-galactosidase adenovirus had no effect (Fig. 3D). We also observed a decrease in KCL-induced insulin secretion that is likely to result from decreased expression of several ion channels (supplemental Table 3).

A decrease in glycolysis would also be predicted to lower malonyl-CoA levels, resulting in increased FFA oxidation (Fig. 4A). As shown in Fig. 4B, Foxo1 increased FFA oxidation 3-fold. Thus, Foxo1 induces a shift from glycolysis to FFA oxidation in β-cells.

**Cytokine Signaling and Urea Cycle**—Cytokine signaling regulates synthesis of NO, a mediator of β-cell damage (36). RNA profiling of Foxo1-expressing β-cells revealed profound changes to this pathway (Table 3). We detected a 6-fold decrease in GTP cyclohydrolase, the rate-limiting enzyme for synthesis of tetrahydrobiopterin, a cofactor required for nitric-oxide synthase activity (37). The Foxo1-induced suppression dovetails with the known stimulatory effect of insulin on expression of this gene (38). Moreover, there were decreases of several enzymes in the urea cycle, which would be expected to decrease the levels of arginine, the NH2 donor for NO synthesis. In this context, the 8-fold decrease of arginase-1, the enzyme that metabolizes arginine to ornithine and urea, is likely to be secondary to decreased substrate synthesis. Although a decrease in arginase levels should lead to increased arginine availability for NO synthesis, it is unclear that this would result in increased NO production, because arginase inhibitors do not affect nitric oxide synthesis in β-cells (39).

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**FIGURE 1.** Overexpression of Foxo1 in INS832/13 cells. A, expression of Foxo1 (ADA) detected by immunoblotting of whole cell extracts. B, Igfbp1 expression detected by reverse transcription-PCR. C, β-cell proliferation, assessed using BrdUrd incorporation, of cells transduced with Foxo1 or β-galactosidase adenovirus. Results represent mean ± S.E. of three separate experiments carried out in triplicate. *, p < 0.05.

**FIGURE 2.** Chromatin immunoprecipitation assays. We isolated intact chromatin from Foxo1-transduced cells and performed immunoprecipitation with control (c) or anti-Foxo1 antiserum (Foxo1). Input DNA is shown in the right-hand lane. We amplified promoter regions spanning Foxo1 binding sites of the Igfbp1, Foxa2, and Isl1 promoters.

**TABLE 1**

Validation of selected changes in gene expression by quantitative PCR

| Gene   | CA-Foxo1 |
|--------|----------|
| Igfbp1 | 5.85 ± 1.4 |
| Creb   | 2.34 ± 0.21 |
| Prkka1 | 2.00 ± 0.19 |
| Myc    | 0.69 ± 0.15 |
| Pdx1   | 0.56 ± 0.09 |
| Cpt1   | 0.42 ± 0.1 |
| Slc2a2 | 0.13 ± 0.03 |
| Foxa2  | 0.13 ± 0.03 |
| Acac   | 0.06 ± 0.02 |
Neurotransmitter Receptors and Monoamine Biosynthesis—Foxo1 induced significant changes in the expression of neurotransmitter receptors and monoamine biosynthetic enzymes (Table 4). We detected increases of mRNAs encoding the cannabinoid receptor-1 and GABA-A receptor β-subunit. Both changes would be predicted to dampen insulin secretion (40, 41), the latter in a glucose-dependent manner (42). It should be noted that activation of cannabinoid-1 and GABA-A receptors in the brain increases food intake (43–45), as does Foxo1 (46). Although we have not yet determined whether Foxo1 regulates these two receptors in the brain, the data are consistent with an overarching Foxo1 function, acting to coordinate β-cell insulin secretion with orexigenic brain signals during fasting.

Foxo1 overexpression also suppressed several enzymes required for monoamine biosynthesis. The most striking change was detected at the \(Ddc\) (DOPA decarboxylase) gene. The functional consequences of these changes in the β-cell are unclear, but it should be noted that \(Ddc\) SNPs are associated with longevity in Drosophila (47) and humans (48).

**Other Pathways Contribute to a Quiescent State of the β-Cell**—Additional, noticeable changes in the transcriptional signature of the Foxo1-overexpressing β-cell include the down-regulation of genes involved in G protein-coupled receptors, including \(Glp1r\) and \(Gipr\); the decrease in the expression of ion channels; and the failure to induce statistically significant changes in genes involved in cell death, survival, and antioxidants. A more detailed description of these changes is presented in the supplemental text and supplemental Tables 2 and 3.

**Table 2**

| Gene symbol | Gene name                                      | Change | p value       |
|-------------|------------------------------------------------|--------|---------------|
| Pklr        | Pyruvate kinase, liver and RBC                 | -11.3  | 6.31E-03      |
| Gpd2        | Glycerol-3-phosphate dehydrogenase 2           | -4.7   | 7.50E-04      |
| Pfkfb2      | Phosphofructokinase/fructose-bisphosphatase 2  | -3.4   | 2.24E-03      |
| Cleebp      | Carbohydrate response element-binding protein  | -3.0   | 2.47E-03      |
| G6p1        | Glucose-6-phosphatase, transport protein 1      | -2.8   | 4.27E-06      |
| Fbp1        | Fructose-1,6-bisphosphatase 1                  | -2.7   | 2.56E-04      |
| Cpt2        | Carnitine palmitoyltransferase 2               | -2.3   | 5.32E-04      |
| Aacs        | Acetoacetyl-CoA synthetase                     | -1.8   | 1.34E-03      |
| Acac        | Acetyl-coenzyme A carboxylase                  | -1.8   | 2.37E-04      |
| Cpt1a       | Carnitine palmitoyltransferase 1, liver        | -1.7   | 4.33E-04      |
| Pfkpm       | Phosphofructokinase, muscle                    | -1.6   | 4.76E-03      |
| Idh1        | Isocitrate dehydrogenase 1                     | -1.5   | 8.90E-04      |
| Acly        | ATP citrate lyase                              | -1.3   | 4.62E-04      |
| Idh3g       | Isocitrate dehydrogenase 3, γ                  | -1.3   | 3.9E-03       |
| Ppkl        | Pyruvate dehydrogenase phosphatase 1           | 1.8    | 1.14E-03      |
| Ldhb        | Lactate dehydrogenase B                        | 1.9    | 4.99E-03      |

**FIGURE 3.** Foxo1 overexpression affects glucose metabolism and insulin secretion. A, diagram of glycolysis. Genes decreased by Foxo1 (Glut2, Gck, F1,6BP, Pfk, and G3pdh) are listed in Table 2. B, glucose oxidation, measured as \(^{14}\)CO\(_2\) production from [U-\(^{14}\)C]glucose. Empty bars denote results of experiments conducted at 2.8 mM glucose; gray bars show results of experiments at 16 mM glucose. C, glucose utilization, measured as \(^{3}\)H\(_2\)O production from [5-\(^{3}\)H]glucose. Results represent mean ± S.E. of three separate experiments performed at least in duplicate. Empty bars, 2.8 mM glucose; gray bars, 16 mM glucose. D, insulin release in the culture medium following incubation in glucose (empty bars, 2.8 mM glucose; gray bars, 16 mM glucose) or KCl (30 mM). Insulin levels are normalized by total protein content. *, p < 0.05; n.s., not significant.
Three conclusions stand out from our analysis of the Foxo1 transcriptional program in pancreatic β-cells: (i) Foxo1 induces a state of metabolic diapause (a response to adverse environment that characterizes a state of metabolic diapause (a response to adverse environment that characterizes a state of metabolic quiescence, with a switch from carbohydrates to lipids as an energy source, a decrease in insulin secretion, and reduced sensitivity to cytokines and cAMP-raising agents. It should be emphasized that this is an exquisitely acute response, since nuclear Foxo1 is rapidly degraded and its levels decline with chronic hyperglycemia (22). Indeed, the metabolic profile of β-cells cultured in high glucose for long periods of time is opposite to that described in this study, with increased expression of glycolytic, lipid synthetic genes (53) and β-cell proliferation (54), consistent with the loss of Foxo1 expression that one would anticipate under those conditions. Alternatively, the changes in gene expression could be interpreted as a “loss of specialized β-cell metabolism” (55). A similar decrease in glycolytic gene expression and glucose/lipid metabolic switch was reported in transgenic mice expressing nuclear Foxo1 in liver (56).

β-Cell Rest as a Target of Diabetes Treatment—Although there is agreement that β-cell failure is central to the onset and steady deterioration of diabetes (7), it is unclear what the treatment of this condition should achieve. β-Cell dysfunction precludes hyperglycemia, and defects of first-phase response to glucose and pulsatility of insulin release can be demonstrated in the preclinical stages of the disease or in mental conditions in which growth, development, and physiological activities are curtailed (49); (ii) arguably, such β-cell rest could be a goal of diabetes treatment; and (iii) Foxo1 targets in β-cells largely differ from canonical diapause targets in Caenorhabditis elegans (50, 51) and show limited overlap with mammalian FoxO1 targets identified by Ramaswami et al. (52) in renal carcinoma cells.

Foxo1 Activation Induces Metabolic Diapause in β-Cells—We have previously shown that Foxo1 nuclear translocation in β-cells is induced by hyperglycemia (22). Hence, this translocation can be construed as part of the physiologic β-cell response to metabolic stress. If so, the transcriptional profile of Foxo1-expressing β-cells should reveal mechanisms underlying this response. The results presented in this study indicate a generalized state of metabolic quiescence, with a switch from carbohydrates to lipids as an energy source, a decrease in insulin secretion, and reduced sensitivity to cytokines and cAMP-raising agents. It should be emphasized that this is an exquisitely acute response, since nuclear Foxo1 is rapidly degraded and its levels decline with chronic hyperglycemia (22). Indeed, the metabolic profile of β-cells cultured in high glucose for long periods of time is opposite to that described in this study, with increased expression of glycolytic, lipid synthetic genes (53) and β-cell proliferation (54), consistent with the loss of Foxo1 expression that one would anticipate under those conditions. Alternatively, the changes in gene expression could be interpreted as a “loss of specialized β-cell metabolism” (55). A similar decrease in glycolytic gene expression and glucose/lipid metabolic switch was reported in transgenic mice expressing nuclear Foxo1 in liver (56).

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### Table 3

| Gene symbol | Gene name                           | Change | p value      |
|-------------|-------------------------------------|--------|--------------|
| Arg1        | Arginase 1                          | −7.8 ± 0.4 | 4.06E-07 |
| Il6r        | Interleukin-6 receptor              | −6.9 ± 1.4 | 1.72E-05 |
| Gch         | GTP cyclohydrolase 1                | −5.9 ± 0.9 | 2.01E-05 |
| Gchfr       | GTP cyclohydrolase I feedback regulatory protein | −5.9 ± 1.0 | 1.88E-03 |
| Cish        | Cytokine-inducible Src homology 2-containing protein | −4.5 ± 2.3 | 4.26E-03 |
| Gatm        | i-Arginine:glycine amidinotransferase | −2.4 ± 0.4 | 2.66E-05 |
| Lito        | LPS-induced tumor necrosis factor-α factor | −2.1 ± 0.2 | 1.94E-04 |
| Ass         | Arginase synthetase                 | −2.0 ± 0.4 | 1.75E-03 |
| Pcd1        | 6-Pyruvyl-tetrahydropterin synthase | −1.9 ± 0.2 | 1.03E-03 |
| Gnip4–18    | Glutamate transporter EAAC1-interacting protein | −1.7 ± 0.2 | 4.15E-05 |
| Gdu1        | Glutamate dehydrogenase 1           | −1.5 ± 0.1 | 2.23E-04 |
| Gltn        | Glutamine synthetase 1              | −1.5 ± 0.1 | 2.38E-04 |
| Asns        | Asparagine synthetase               | −1.4 ± 0.1 | 2.12E-03 |
| Slc25a11    | 2-Oxoglutarate carrier              | −1.4 ± 0.1 | 4.19E-03 |
| Mibfd1      | C1-tetrahydrofolate synthase        | 1.5 ± 0.5 | 1.35E-04 |
| Adam1       | A disintegrin and metalloproteinase domain 1 | 1.6 ± 0.2 | 6.56E-03 |
| Odc1        | Ornithine decarboxylase 1           | 1.6 ± 0.1 | 9.29E-04 |
| Hyp1        | Hypoxanthine guanine phosphoribosyl transferase | 1.6 ± 0.1 | 1.81E-03 |
| Gucy1B3     | Guanylate cyclase 1, soluble, β3    | 2.3 ± 0.3 | 2.49E-04 |
unaffected relatives of diabetic patients (4, 57). Treatment with sulfonylureas leads to partial restoration of insulin response (58–62), but it remains unclear whether β-cell function can be rendered normal. Moreover, the high rates of primary and secondary failure associated with drugs targeting β-cell dysfunction, such as sulfonylureas, have raised concerns that these agents accelerate β-cell failure. But the results of the United Kingdom Prevention of Diabetes Study appear not to substantiate these concerns, since the rates of failure of monotherapy were similar in patients treated with sulfonylureas or metformin (63). The introduction of new “β-tropic” drugs, such as incretins and DPP-4 inhibitors, with a distinct mechanism of action, is promising in this regard, but it should be emphasized that these drugs have modest effects (average HbA1c reductions ≤1%) (8). It has been suggested that a therapeutic goal, at least in the initial phases of the disease, should be the induction of a state of dauer—a physiologic response to nutrient availability. Regulation of Foxo1 activity is a promising, if challenging, approach to diabetes treatment.

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TABLE 4
Neurotransmitter receptors and monoamine synthetic pathway

| Gene symbol | Gene name | Change | p value |
|-------------|-----------|--------|---------|
| Cnr1        | Cannabinoid receptor 1 | 3.6 ± 0.9 | 8.62E-04 |
| Glra3       | Glycine receptor, a3 | 2.7 ± 0.7 | 4.52E-03 |
| GabaR1      | GABA A receptor, y1 | 2.4 ± 0.4 | 8.41E-04 |
| Oprs1       | Opioid receptor, α1 | 1.9 ± 0.2 | 9.58E-05 |
| Gfra2       | Gial-derived neurotrophic factor receptor α2 | 1.8 ± 0.1 | 5.62E-03 |
| Glrb        | Glycine receptor, β subunit | 1.8 ± 0.2 | 2.53E-03 |
| Cript       | Postsynaptic protein Cript | 1.7 ± 0.2 | 4.78E-04 |
| Grin1la     | Glutamate receptor, ionotropic | 1.2 ± 0.0 | 2.71E-04 |
| Glud1       | Glutamate dehydrogenase 1 | −1.5 ± 0.1 | 2.23E-04 |
| Glyhr        | Gephyrin | −1.6 ± 0.1 | 1.64E-03 |
| Maob        | Monoamine oxidase B | −1.7 ± 0.3 | 5.15E-03 |
| Th          | Tyrosine hydroxylase | −2.0 ± 0.5 | 5.12E-03 |
| Necab2      | Neuronal calcium binding 2 | −2.7 ± 0.2 | 1.12E-04 |
| Gad1        | Glutamate decarboxylase 1 | −4.0 ± 0.6 | 1.80E-06 |
| Ddc         | DOPA decarboxylase | −5.2 ± 0.4 | 9.49E-04 |

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Foxo1 and β-Cell Function
