**SUPPLEMENTARY MATERIAL:**

**Human subject recruitment:** All procedures were approved by Einstein’s Institutional Review Board. The purpose, nature, risks, benefits and procedures of the study were explained to all potential subjects and their voluntary, informed, written consent was obtained. All subjects completed a clinical screening evaluation consisting of medical history, physical examination, and laboratory evaluation including hematologic, lipid, and chemistry parameters (including fasting glucose level), and baseline electrocardiogram.

**Rats:** A total of fifty-four studies were performed on 12-14 week-old male Sprague Dawley rats (Charles River Breeding Laboratories). Pilot studies were performed on thirty-five of these rats, to assess appropriate time course, glucose levels, and optimal glyburide and diazoxide doses. Nineteen rats with an average weight of 386.1 ± 7.2 g were studied under the following conditions: 1. Oral (gavage) normal saline control (NS, n=7).

2. Oral (gavage) Glyburide (GLB, n=7).

3. Oral (gavage) Glyburide with intracerebroventricular (ICV) infusion of the KATP channel activator blocker Diazoxide (GLB+DZX, n=5).

Twenty minutes prior to a four-hour pancreatic clamp study, rats matched for age and weight received oral normal saline (NS) or 2.5 mg/kg of Glyburide (GLB) by gavage in parallel with the human studies (Figure A). To determine whether the effects of oral glyburide on EGP are mediated through central mechanisms, a third group of rats received the same dose of oral glyburide with an ICV infusion of the KATP channel activator Diazoxide (GLB+DZX, 9.6 mg/dl) two hours prior to the pancreatic clamp study (Figure 2B). As previously described, rats were prepared for the in vivo experiments with implantation of an ICV cannula under anesthesia occurred two weeks prior to the study and implantation of carotid and internal jugular catheters occurred one week prior (1,2).

**Intracerebroventricular (ICV) Cannulation:**

Three weeks prior to the clamp studies, all ICV cannulae were implanted into the third cerebral ventricle by stereotaxic surgery, performed in Einstein’s Chronobiosis and Aging/Metabolism of Aging (CEAC) animal care facility following the well-designed and histologically verified methodology developed by Rossetti’s group (3, 4, 5, 6).

Specifically, each rat was fixed in a KOPF stereotaxic apparatus (DAVID KOPF INSTRUMENT, Tujunga, CA) with ear bars and a nose piece set at +5.0 mm. A 22-gauge stainless steel guide cannula (C313GSPCXC, Plastics One, Roanoke, VA) was chronically implanted into the third ventricle using the following coordinates from bregma: anterior-posterior; +0.2 mm, dorsal-ventral; −9.0 mm, medial-lateral; 0.0 directly on the midsagittal suture. A mating dummy cannula (C313DC/SPC, Plastics One, Roanoke, VA) was inserted to prevent clogging of the guide cannula. The implant is secured to the skull with dental cement, and the skin is closed over the implant using wound clips. All surgeries were performed under anesthesia by intraperitoneal ketamine (Ketaset, 87 mg/kg) and xylazine (Rompun, 11 mg/kg). Recovery was monitored until body weight was within 3% of the pre-operative weight (5–6 days). Intravenous infusion of diazoxide or saline was performed as described (2). Following the studies, the established methodology included verification of implantation histologically for each animal, as described (2).

**Supplementary Table 1**

Forward and reverse primer sequences for the gluconeogenic enzymes phosphoenolpyruvate carboxykinase (*Pepck*), glucose-6-phosphatase (*G6pase*), and five housekeeping genes (*B2m, Rpl19, Gapdh, βactin, 18s*).

|  |  |  |
| --- | --- | --- |
| Genes | Forward Sequence | Reverse Sequence |
| Rat *Pepck* | GGAAAGACAAAAACGGCAAG | ACGTAGCCAATGGGAGTGAG |
| Rat *G6pase* | TGCTGCATCTCTTTGACTCG | TTGTGTGTCTGTCCCAGGAG |
| Rat *B2m* | CTGCTACGTGTCTCAGTTCCAC | TGCAAGCATATACATCGGTCTC |
| Rat *Rpl19* | GACCTGGATGCGAAGGATGA | CCATGAGAATCCGCTTGTTT |
| Rat *Gapdh* | AAACCCATCACCATCTTCCA | GTGGTTCACACCCATCACAA |
| Rat *βactin* | GCTACAGCTTCACCACCACA | AGGAAGGAAGGCTGGAAGAG |
| Rat *18s* | AGGGTTCGATTCCGGAGAGG | CAACTTTAATATACGCTATTGG |
|  |

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