

		Blood Glucose (mmol/L)						Blood BHB (mmol/L)					
		Day 1		Day 2		Day 3		Day 1		Day 2		Day 3	
		0min	120min	0min	120min	0min	120min	0min	120min	0min	120min	0min	120min
Non-D Chow	No Hypo (n=5)	6.1±0.19	5.6±0.2	6.0±0.08	5.7±0.2	5.7±0.07	5.7±0.2	0.4±0.05	0.5±0.06	0.4±0.04	0.5±0.07	0.4±0.00	0.5±0.05
	1x-Hypo (n=5)	5.8±0.21	5.8±0.3	5.4±0.16	5.8±0.14	5.7±0.23	1.6±0.18*	0.5±0.11	0.5±0.05	0.5±0.05	0.6±0.06	0.4±0.04	0.4±0.03
	3x-Hypo (n=5)	5.7±0.29	2.4±0.66*	5.9±0.33	1.8±0.23*	5.8±0.18	1.6±0.17*	0.4±0.04	0.5±0.05	0.5±0.06	0.5±0.06	0.4±0.05	0.4±0.05
Non-D Keto	No Hypo (n=5)	4.5±0.37	5.0±0.28	5.0±0.25	5.3±0.17	5.0±0.34	5.1±0.22	3.5±0.44	2.5±0.34	2.7±0.29	2.1±0.19	2.2±0.35	2.3±0.54
	1x-Hypo (n=7)	4.2±0.10	4.9±0.21	4.3±0.33	5.3±0.29	4.9±0.36	1.4±0.17*	3.3±0.26	2.7±0.28	3.8±0.63	2.6±0.43	2.7±0.42	0.9±0.08
	3x-Hypo (n=5)	4.9±0.34	1.5±0.20*	4.2±0.32	2.1±0.38*	4.1±0.52	1.9±0.16*	2.9±0.29	1.1±0.2*	4.0±0.8	2.8±1.02	4.0±0.79	1.5±0.15*
STZ-D Chow	No Hypo (n=5)	9.1±2.26	6.8±2.08	9.1±2.98	7.2±1.82	10.3±2.36	7.7±2.09	0.4±0.02	0.4±0.04	0.4±0.03	0.4±0.03	0.4±0.05	0.4±0.03
	1x-Hypo (n=5)	12.7±3.29	9.7±2.76	13.0±2.89	9.2±2.09	11.4±3.41	2.6±0.31*	0.4±0.03	0.4±0.07	0.4±0.04	0.4±0.02	0.4±0.04	0.4±0.05
	3x-Hypo (n=4)	10.7±4.93	2.6±0.27	11.9±3.01	2.3±0.48	11.8±2.25	2.2±0.24	0.4±0.05	0.3±0.06	0.3±0.03	0.3±0.05	0.3±0.04	0.4±0.12
STZ-D Keto	No Hypo (n=5)	10.1±2.41	9.8±2.36	10.7±2.86	10.3±1.91	11.2±1.97	10.8±1.85	3.8±1.30	3.9±1.53	4.3±1.41	3.3±1.09	3.2±1.11	3.6±1.43
	1x-Hypo (n=5)	13.4±2.98	12.4±2.53	11.9±2.61	12.1±2.46	12.6±2.54	2.7±0.22*	5.0±1.08	5.0±1.32	5.6±1.08	5.1±1.01	4.2±1.07	0.8±0.12*
	3x-Hypo (n=5)	12.8±4.34	2.9±0.68*	9.9±2.18	2.1±0.19*	10.5±2.54	2.2±0.13*	5.0±1.22	2.4±0.74	4.9±1.15	2.0±0.79	5.1±0.67	1.4±0.22*

Table S1. Blood glucose (BG) and β-hydroxybutyrate (BHB) before (0min) and after (120min) insulin (or vehicle) injection.

Data are mean ± SEM, *p < 0.05 vs 0min.

Figure S1

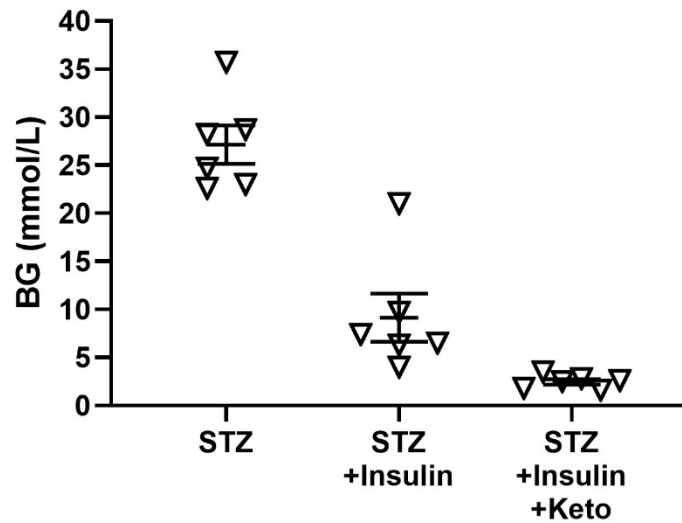


Figure S1. Insulin supplementation in STZ-D Keto-fed rats induced profound hypoglycemia. Following the induction of diabetes with STZ, rats ($n = 6$) were implanted with 1-2 continuous-release insulin pellets which reduced hyperglycemia within 48 h (STZ+Insulin). When subjected to a keto diet, all rats in the group became hypoglycemic within the first week of feeding (STZ+Insulin+Keto). The diet was replaced with the standard chow and animals were excluded from the study.

Figure S2

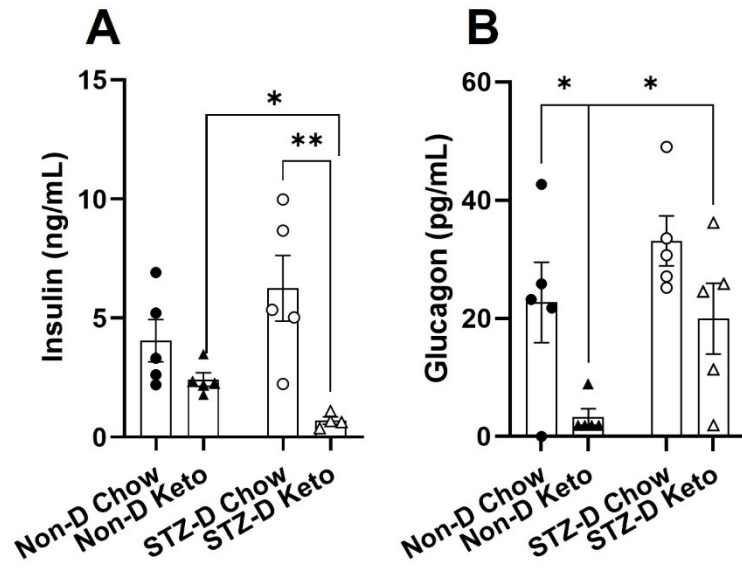


Figure S2. Differential changes in circulating insulin and glucagon in non-diabetic and diabetic rats. Plasma insulin and glucagon were measured in animals not subjected to hypoglycemia (No Hypo groups) to estimate the baseline levels under non-diabetic and diabetic conditions and assess the effects of diet-induced ketosis on both. A) STZ-D Keto-fed rats had significantly lower insulin than Non-D Keto-rats ($p < 0.05$) and STZ-D Chow-fed rats ($p < 0.01$); B) Baseline glucagon in Non-D Keto-fed rats was significantly lower than in Non-D Chow rats and STZ-D Keto rats ($p < 0.05$).

Figure S3

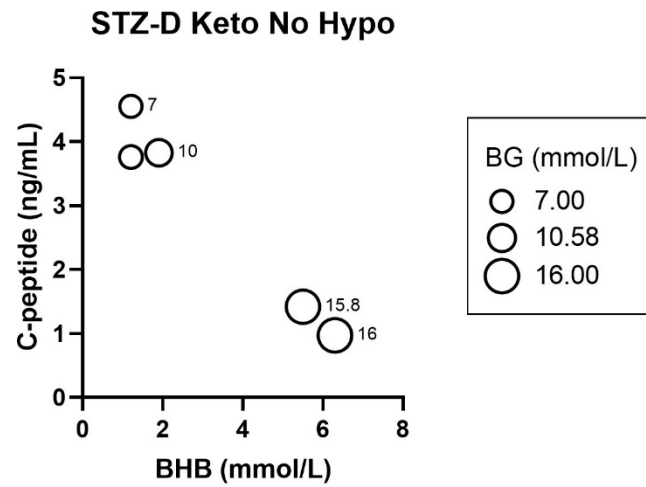


Figure S3. C-peptide concentration inversely related to BG and BHB. Plasma C-peptide was measured in STZ-D Keto-fed rats from the No Hypo group. Animals with highest BG and BHB had the lowest C-peptide concentration. The size of the circles indicates BG concentration and numbers show individual values.