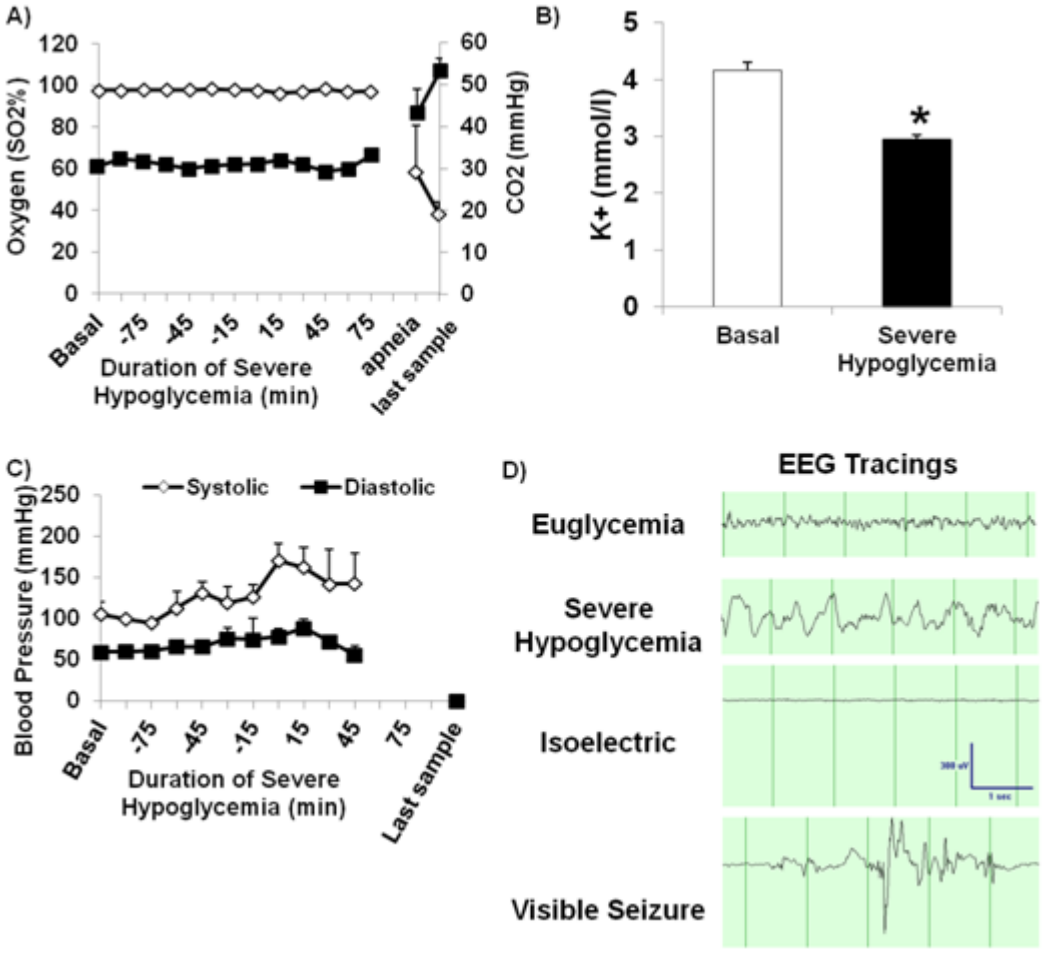
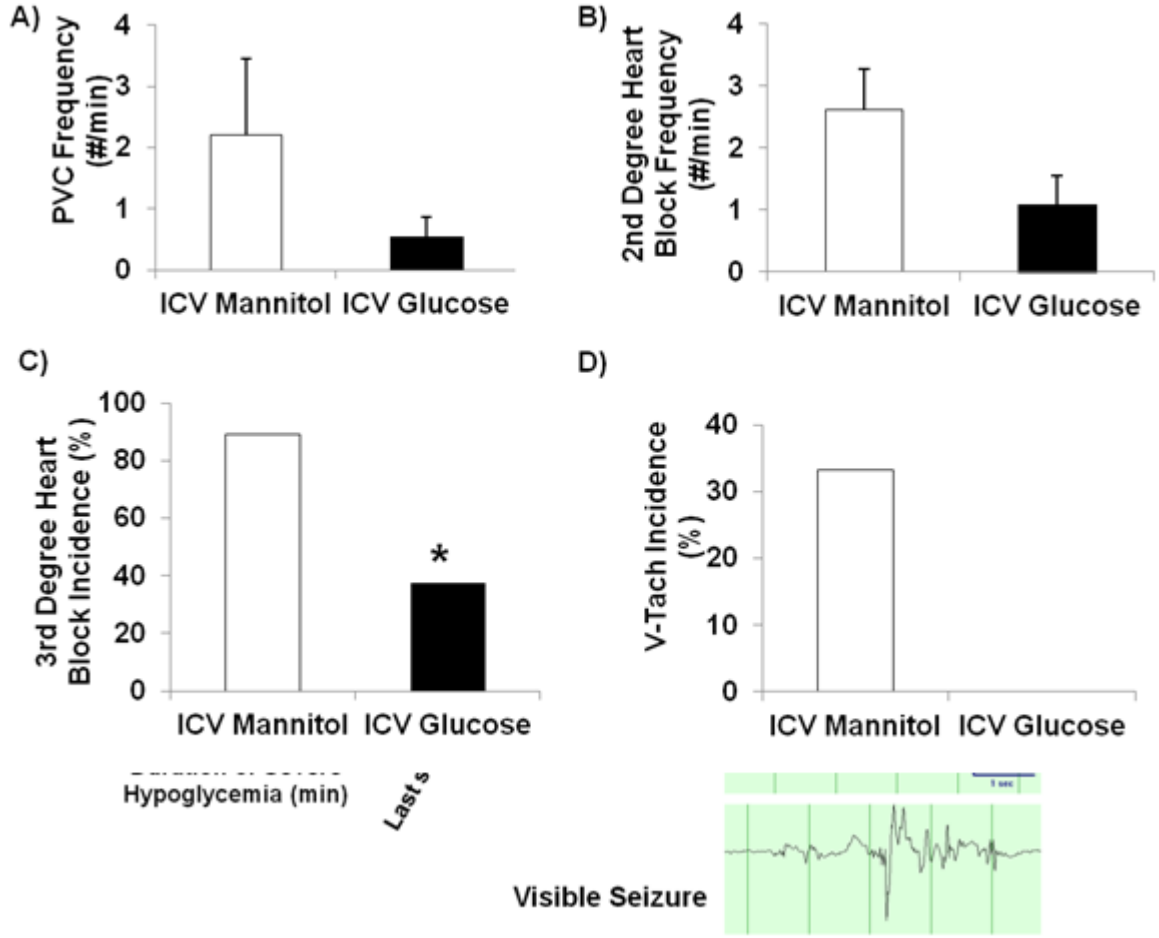
SUPPLEMENTARY DATA

Supplementary Figure 1. Blood gas, blood pressure, and EEG tracings during severe hypoglycemia in control experiments (study 3). A) Oxygen (open diamond, left axis) and carbon dioxide (black square, right axis) levels remain normal during severe hypoglycemia (97% O2 and 32 mmHg CO2). During apnea and just prior to death, oxygen levels decrease (38±6%) and carbon dioxide levels increase (53±3 mmHg). B) Potassium fell from 4.16±0.15 mmol/l in the basal state to 2.96±0.06 mmol/l during severe hypoglycemia. (*p<0.001, ttest) C) Blood pressure increased at the start of severe hypoglycemia and remained elevated throughout severe hypoglycemia. Blood pressure decreased as the rats died. D) The progressive series of EEG recordings initially shows basal brain activity during the euglycemic state followed by slow, high amplitude brain waves, characteristic of severe hypoglycemia. Isoelectric activity on the EEG corresponded to rats in a comatose state. The sudden onset of chaotic, high amplitude EEG voltages of short duration (~5 seconds) corresponded to visible tonic-clonic seizure-like behavior. n=6. Data expressed as mean±sem.



SUPPLEMENTARY DATA

Supplementary Figure 2. Arrhythmia incidence in ICV glucose infusion (study 4). A) During severe hypoglycemia, the frequency of premature ventricular contractions (PVCs) was nonsignificantly reduced in ICV glucose (0.54±0.32/minute) compared to ICV mannitol (2.2±1.2/minute) infused rats (p = 0.07). B) During severe hypoglycemia, frequency of 2nd degree heart block was not different between the groups (ICV mannitol: 2.6±0.66/minute; ICV glucose: 1.1±0.45/minute). C) Incidence of 3rd degree heart block during hypoglycemia was 89% and 38% for the ICV mannitol and ICV glucose infused rats, respectively (*p<0.05). D) Ventricular tachycardia (v-tach) during severe hypoglycemia occurred in 38% of the ICV mannitol and 0% of the ICV glucose infused rats (p=NS). *p<0.05, ttest. n=9/group. Data expressed as mean±sem.



SUPPLEMENTARY DATA

Supplementary Figure 3. Insulin levels, mortality incidence and blood pressure levels during severe hypoglycemia with or without adrenergic blockade (study 5). A) Insulin levels were not different among the groups in the basal or severe hypoglycemia periods. B) Incidence of severe hypoglycemia induced death was increased with duration of sinus tachycardia (defined as >400BPM). Tachycardia did not develop in α/β or β blocker rats. Alpha blockade rats all died with less than 15 minutes of tachycardia whereas control rats had 100% mortality with more than 30 minutes of tachycardia. C) Incidence of mortality increased with QTc length. During severe hypoglycemia, rats that had a QTc prolongation of 150-179ms all survived, whereas in rats where hypoglycemia increased QTc lengths to 180-200ms there was an associated increase in mortality to 25% in control rats. In control and alpha blockade rats, QTc prolongation of more than 200ms resulted in 33% and 67% mortality, respectively. D and E) Systolic (D) and diastolic (E) blood pressure (BP) during severe hypoglycemia were lower in β blocker infused rats compared to controls (*p<0.001 Two-way ANOVA). White bar= control; black bar= α/β (a/b) blocker; diagonal slash= α (a) blocker; horizontal slash= β (b) blocker. n=5-13. Data expressed as mean±sem.