**Supplementary Data**

Supplementary Figure 1. Verification of the mouse model of hypoglycemia awareness/unawareness. The timeline is depicted at the top of the figure. A/B. The time in seconds (s) was measured for the least-preferred chamber of the conditioned place preference (CPP) box immediately following habituation to the box (Pre), after conditioning the mice to Froot Loops™ in that chamber (post-conditioning, PC), and after the mice received an injection of insulin in the food-associated chamber (post-conditioning injection, PC-I). Mice received daily injections of (A) saline (RS; N = 8) or (B) insulin (RH; N = 10) for 3 days in their home cage after conditioning and before the insulin injection in the food-associated chamber. Data were analyzed by repeated measures one-way ANOVA followed by Tukey’s multiple comparison test. Different letters are significantly different (P<0.05). Successful conditioning is indicated by a significant increase in the time PC compared to Pre. RS mice reduced the time in the food-associated chamber after receiving an insulin injection in that chamber, whereas RH mice did not (PC-I vs PC). C. The percentage of time spent in the food-associated chamber after the insulin injection for RS and RH mice. RH mice spent significantly less time in the food-associated chamber after injection than RH mice (unpaired Students t-test, P < 0.05). D. An additional cohort of mice were injected with saline instead of insulin in the food-associated chamber. These mice were successfully conditioned (P < 0.05, paired Students t-test); however, they did not reverse their preference for the food-associated chamber after receiving a saline injection in this chamber (P = 0.361, repeated measures one-way ANOVA). E. Percent change in time spent in the food-associated chamber before and after insulin injection (PC-I vs PC) was not statistically different from a theoretical mean of zero (P = 0.59, one sample t-test, N = 7). All data presented as individual values shown with mean and SD. Different letters represent statistical differences (P<0.05).

**Supplementary Data**

*Verification of the mouse model*. Otlivanchik et al. developed the behavioral model for hypoglycemia awareness/unawareness in the rat (7). Thus, it was necessary to establish the model in the mouse for consistency with the electrophysiological studies using transgenic orexin-GFP mice. Both Otlivanchik (7,50) and our previous studies (42) used chocolate drops to establish CPP in rats. Unlike rats, the mice did not develop a CPP using chocolate drops. Instead, we found that placing Froot Loops™ cereal in the designated food-associated chamber successfully established a CPP for that chamber as shown in Supplementary Figure 1A, B and D. While Froot Loops™ are sweeter than chocolate chips, our results are unlikely to be due to a change in sweetness sensitivity after RH because the animals are trained prior to RH exposed and are not exposed to Froot Loops ™ again after RH. There was a significant increase in time spent in the food-associated chamber (post-conditioning [PC] vs pre-conditioning [Pre]). Figure 4A and C shows that mice which received 3 daily saline injections (RS) in their home cage followed by insulin-induced hypoglycemia in the food-associated chamber reversed their preference for that chamber (post-conditioning injection [PC-I] vs PC). In contrast, mice receiving 3 daily insulin injections (RH) did not (Figure 1B and C). In order to demonstrate that the injection itself in the food-associated chamber was not aversive, a subgroup of mice that received a saline injection in the food-associated chamber did not reverse their preference for that chamber (Figure 1D and E).

We made several anecdotal observations regarding strain differences between C57Bl/6N mice from Charles River Laboratories and C57Bl/6J mice from The Jackson Laboratory while establishing the model in mice. We are reporting these observations for transparency, reproducibility, and rigor. We initially attempted to establish the mouse model using singly housed C57Bl/6N mice from Charles River Laboratories due to the potential interaction between social factors and the orexin system (51). However, we were unable to induce conditioning. Surprisingly, we were also unable to produce reliable insulin-induced hypoglycemia even with very high doses of insulin. Group housing improved results but did not lead to a viable model. We then evaluated C57Bl/6J mice obtained from The Jackson Laboratory. Although results were much improved compared to C56Bl/6N mice, we were unable to reliably produce conditioning or hypoglycemia in singly housed mice. However, we succeeded (Figure 1) in producing conditioning and hypoglycemia awareness/unawareness when C57Bl/6J mice from The Jackson Laboratory were group housed. These mice were used for all subsequent behavioral experiments.