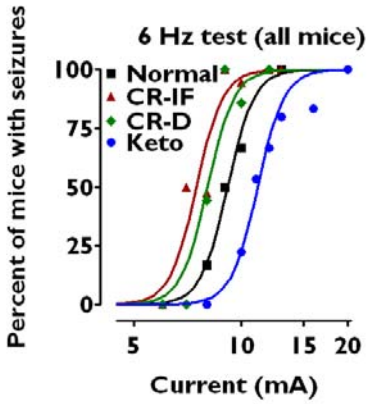
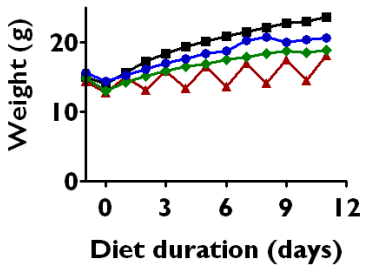
A



B

Diet	CC50 mA (95% confid. limit)
Normal	9.32 (8.59-10.1)
CR-IF	7.73 (7.16-8.31)**
CR-D	8.16 (7.42-8.90)*
Keto	11.4 (10.8-12.1)***
*P = 0.03, **P = 0.001, ***P < 0.001 versus Normal	

C



D

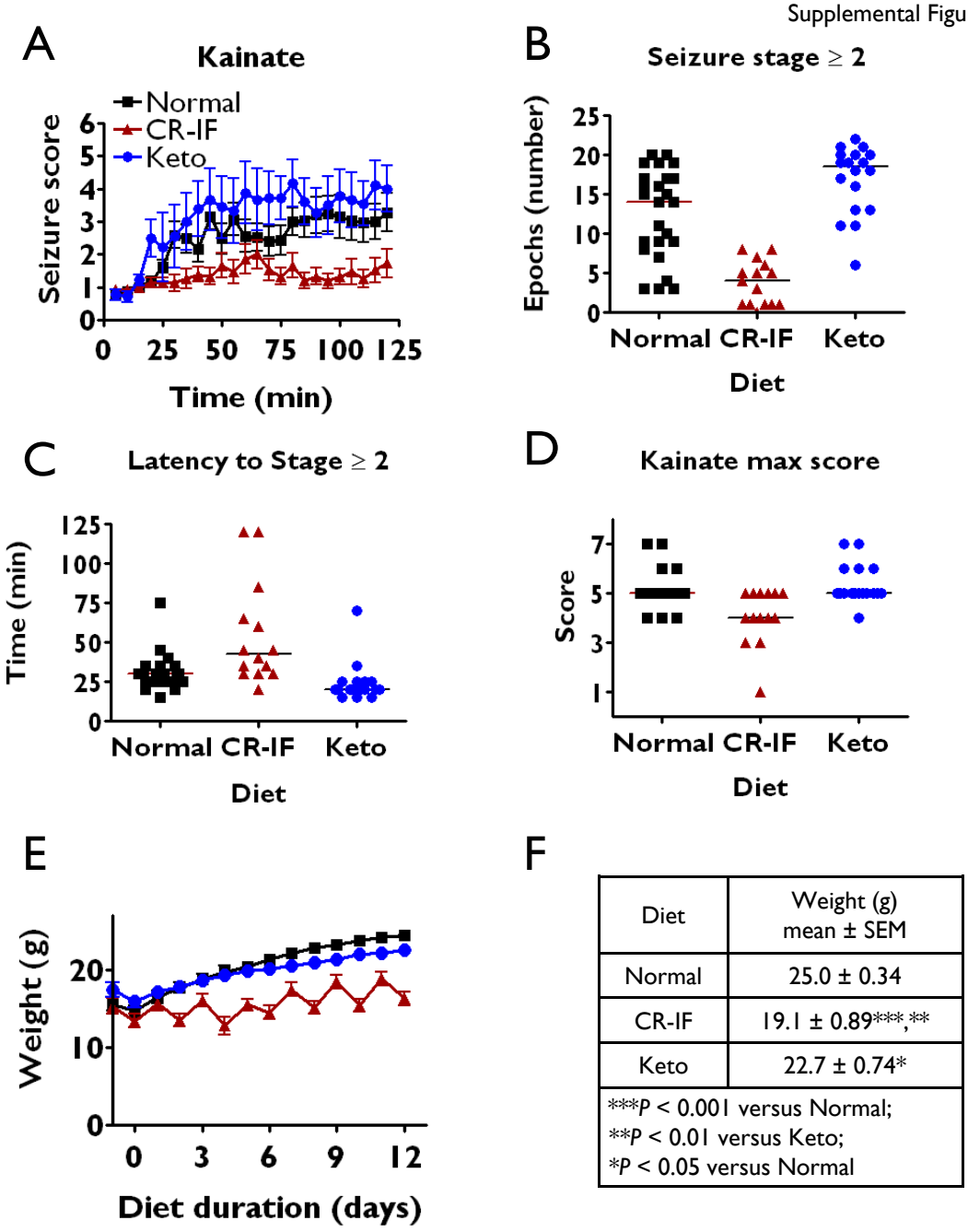
Diet	Weight (g) mean ± SEM
Normal	24.3 ± 0.20
CR-IF	18.8 ± 0.27*,***
CR-D	18.9 ± 0.24*, **
Keto	20.3 ± 0.35*
*P < 0.001 versus Normal; ***P < 0.001 versus Keto; **P < 0.01 versus Keto	

E

Probit analysis of seizure thresholds comparing animals within each diet group that are above (A) versus below (B) mean weight:

Keto: A = 11.4 mA (10.1-12.8), B = 11.4 mA (9.94-12.8); P = 0.96
CR-IF: A=8.08 mA (7.38-8.78), B = 7.47 mA (6.76-8.18); P = 0.23
CR-D: A = 8.53 mA (7.90-9.17), B = 8.09 mA (7.21-8.93); P=0.38

Figure S1. Calorie restriction (intermittent and daily) and the ketogenic diet have opposite effects on 6 Hz-induced seizures. (A) Probability of seizure events at the indicated currents was determined by a probit analysis. Results presented are for all mice fed normal rodent chow without restriction (Norm, n = 43 mice), mice fasted (24h) and fed unrestricted normal rodent chow (24h) on alternate days (CR-IF, n = 72), mice fed restricted amounts of normal rodent chow daily (CR-D, n = 44), and mice fed the ketogenic diet (Keto, n = 58), tested in 3-4 independent animal cohorts in 3-4 independent experiments. Because the curves shown represent a probability function, not all points lie on the curve. (B) The current where 50% of mice had convulsions (CC50) was derived from data in panel A. (C) Weights of animals shown in panel A through day 11 (before animals were removed from each set for testing on days 11-13). (D) Body weights on the day of seizure testing for all mice in panel A, mean +SEM; analyzed by one-way ANOVA with Tukey's multiple comparison test. (E) Probit analysis of seizure thresholds comparing animals within each diet group that are above (A) versus below (B) mean weight.

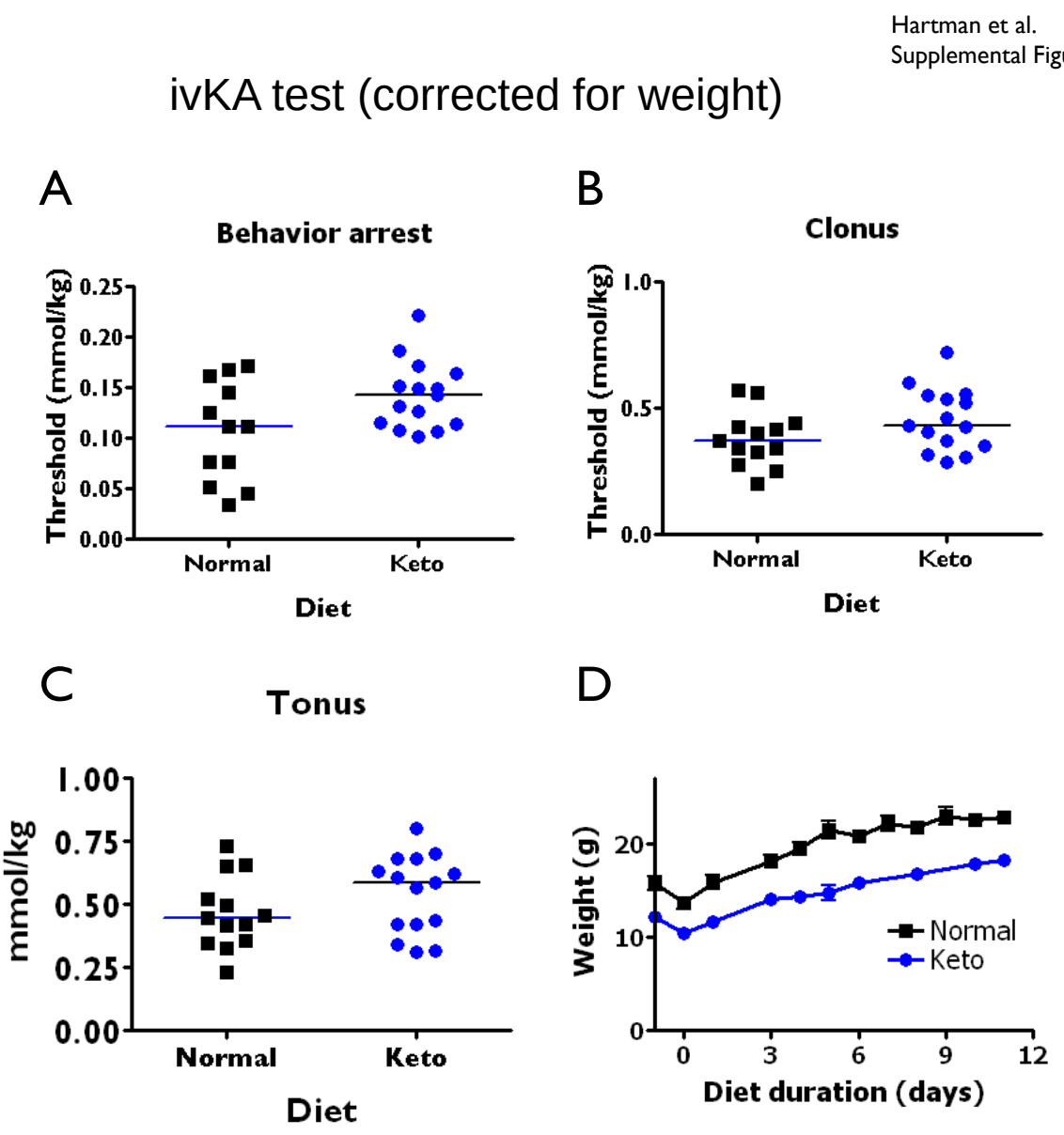


F

Diet	Weight (g) mean ± SEM
Normal	25.0 ± 0.34
CR-IF	19.1 ± 0.89***,**
Keto	22.7 ± 0.74*

***P < 0.001 versus Normal;
**P < 0.01 versus Keto;
*P < 0.05 versus Normal

Figure S2. Intermittent fasting (CR-IF), but not the ketogenic diet, protects against seizures induced by kainic acid injected intraperitoneally (ip). (A) Mean seizure scores (+SEM) were assessed in 5 min blocks for two groups of all mice tested independently. Mice were fed as described for Figure 1; (Norm, n = 25 mice; CR-IF, n = 14; Keto, n = 18). (B) Number of 5-min blocks spent in seizure stage ≥ 2 for animals in panel A (Normal versus CR-IF & CR-IF versus Keto, $P < 0.001$; Normal versus Keto, $P < 0.05$; analyzed by one-way ANOVA with Tukey's multiple comparison test). Bar represents the group median. (C) Latency to seizure score ≥ 2 (bar represents group median) for animals in panel A (Normal versus CR-IF & Normal versus Keto, $P < 0.05$; CR-IF versus Keto, $P < 0.001$; analyzed by Kruskal-Wallis test with Dunn's multiple comparison test). Bar represents the group median. (D) Maximum seizure scores for mice in panel A (CR-IF versus Keto, $P < 0.001$; Normal versus CR-IF, $P < 0.01$; Normal versus Keto, $P > 0.05$; analyzed by Kruskal-Wallis test with Dunn's multiple comparison test). Bar represents the group median. (E) Weight of animals shown in panel A (until the first animals were removed for seizure testing). (F) Body weights on the day of seizure testing for mice in panel A, mean +SEM; analyzed by one-way ANOVA with Tukey's multiple comparison test.



E

Diet	Weight (g) mean ± SEM
Normal	22.5 ± 0.9
Keto	19.9 ± 0.70*
*P = 0.003	

Figure S3. The ketogenic diet does not protect against iv kainic acid-induced seizures. (A) Threshold dose for behavior arrest (A), clonus (B), and tonus (C) (P = 0.03 for behavior arrest but P > 0.05 for others). Bars show the median for each group. Results presented are for mice fed as described in Figure 1 (Normal, n = 13 mice; CR-IF, n = 15), tested in 3 independent experiments. (D) Weights of animals shown in panels A-C (before animals were removed from each set for testing on days 11-17). (E) Body weights on the day of seizure testing for mice in panels A-C, mean +SEM; analyzed by Student's *t* test.

ivKA test (not corrected for weight)

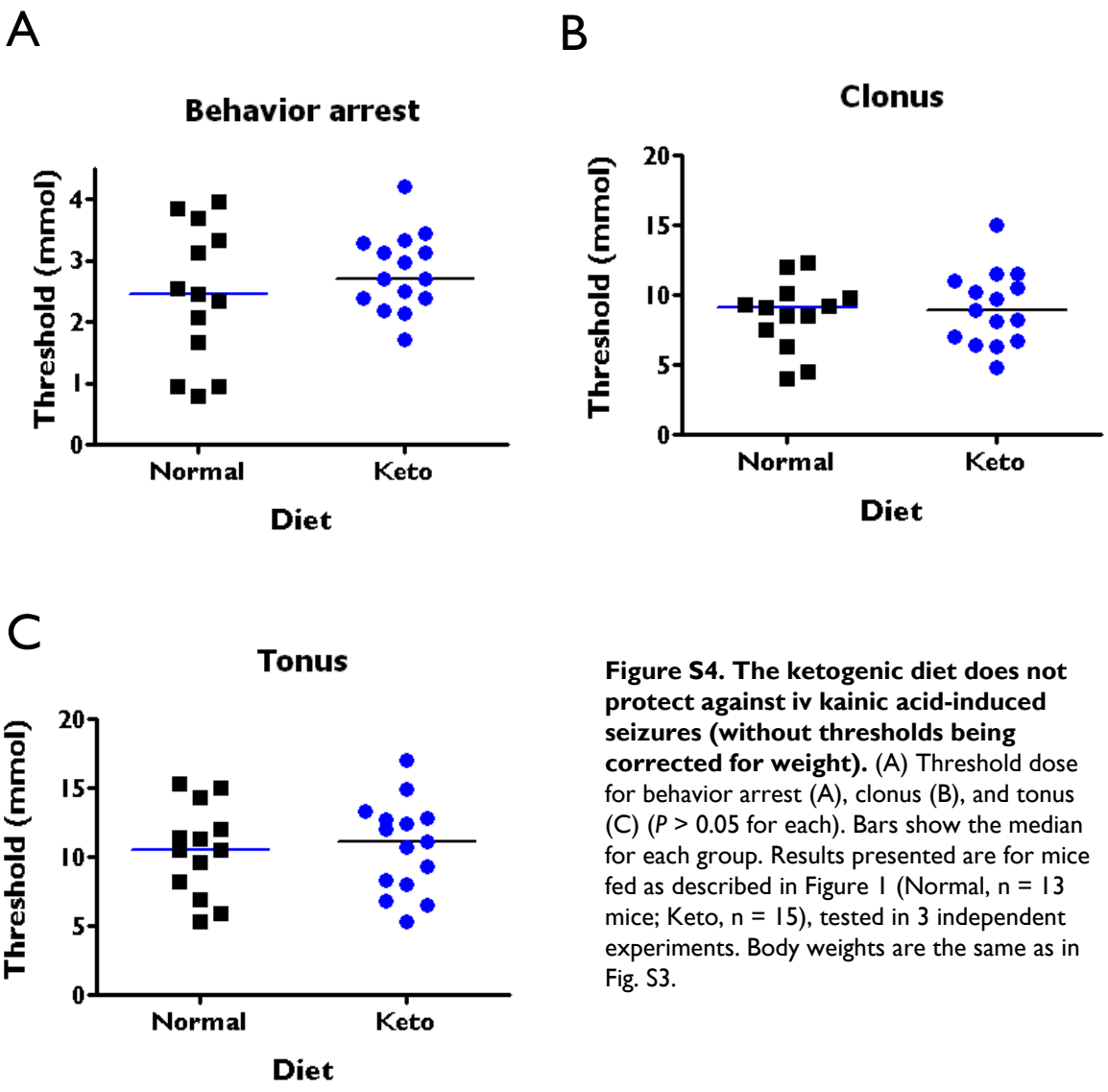
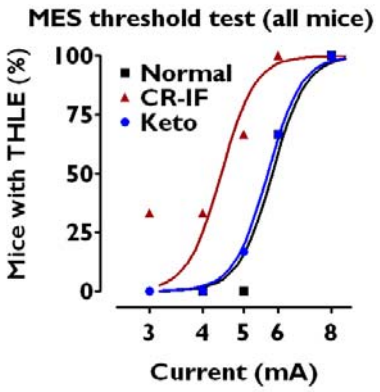


Figure S4. The ketogenic diet does not protect against iv kainic acid-induced seizures (without thresholds being corrected for weight). (A) Threshold dose for behavior arrest (A), clonus (B), and tonus (C) ($P > 0.05$ for each). Bars show the median for each group. Results presented are for mice fed as described in Figure 1 (Normal, n = 13 mice; Keto, n = 15), tested in 3 independent experiments. Body weights are the same as in Fig. S3.

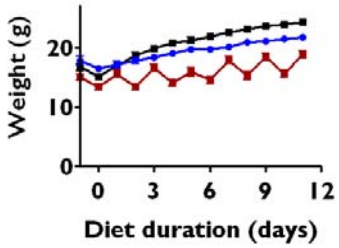
A



B

Diet	C-THLE50 mA (95% confid. lim.)
Normal	5.97 (5.42-6.52)
CR-IF	4.12 (3.59-4.66)*
Keto	5.75 (5.12-6.39)†
*P < 0.001 versus Normal; †P = 0.61 versus Normal	

C



D

Diet	Weight (g) mean ± SEM
Normal	24.5 ± 0.32
CR-IF	19.0 ± 0.63*
Keto	22.1 ± 0.42*
*P < 0.001 for all comparisons	

Figure S5. Intermittent fasting is detrimental in the MES test. (A) Probability of seizure events at the indicated currents was determined for all mice by a probit analysis. Results presented are for 3 independent animal cohorts in 3 independent experiments (Norm, n = 33 mice; CR-IF, n = 24; Keto, n = 29). Because the curves shown represent a probability function, not all points lie on the curve. (B) The current where 50% of mice had tonic hindlimb extension (C-THLE50) was derived from data in panel A. (C) Weights of animals shown in panel A (before animals were removed from each set for testing on days 10-15). (D) Body weights on the day of seizure testing for mice in panel A, mean +SEM; analyzed by one-way ANOVA with Tukey's multiple comparison test.