Paraventricular opioids alter intake of high-fat but not high-sucrose diet depending on diet preference in a binge model of feeding

Naleid, A. M., Grace, M. K., Chimukangara, M., Billington, C. J., & Levine, A. S. (2007). Paraventricular opioids alter intake of high-fat but not high-sucrose diet depending on diet preference in a binge model of feeding. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 293(1), R99–R105. https://doi.org/10.1152/ajpregu.00675.2006

This study 'confronts' to lines of evidence

- Determine the nuances of opioid control of feeding
  - "one peptide, one nutrient"
  - opioids modulate intake of a preferred diet, but not of a non-preferred diet

However previous data had potential confounds

- methods to stimulate intake were either: (a) deprivation, (b) restriction of intake or (c) drug-stimulation

To account for that, they used a 'binge eating model'

- animals will eat significant amounts of food, even when satiated, if the presentation of snacks are unpredictable and at the end of the light cycle (limiting access to fatty-food or high-sucrose) (Naleid et al., 2007)
- this allows to model 'spontaneous feeding' (more similar to human-type feeding)

Having a feeding model, they attempted to clarify opioid control of feeding

- They used PVN (paraventricular nucleus) as a site for testing the effects of opioids in the choice of two palatable diets (fat or sucrose)
- Also, they tested this model against the previous ones (deprivation-induced feeding)

Opioids and opioid antagonist used

- Naltrexone (NTX): opioid antagonist
  - 0, 10, 30 and 100 nmol)
  - intra-PVN / subcutaneously
- DAMGO: sythetic opioid, high affinity to mu-receptor
  - intra-PVN
  - 0, 0.025, 0.25 and 2.5 nmol)

The experimental setup (diet-choice experiment)

- continual access to standard rodent chow and water
- after surgery recovery they were presented with a jar of fat diet and pellets of AIN 76 (sucrose)
- presentation was in their home cages for 3h a day, water was available but chow was blocked
- counterbalanced, repeated measures

The experimental setup (diet-choice experiment)

Table 1. *Composition of diets used in the study*

Components	Diet Weight, %	
	High Sucrose	High Fat
Cornstarch	13.8	0
Sucrose	50	0
Casein	21.2	32.9
DL-Methionine	0.3	0.4
Choline chloride	0.2	0.3
Vitamin mix	1	1.5
Mineral mix	3.5	5.4
Cellulose	5	7.8
Corn oil	5	7.8
Shortening	0	43.9
Kcal/g	3.90	6.03
Fat energy, %	11.54	77
Carbohydrate energy, %	68.64	3.2
Protein energy, %	19.6	19.6

Vitamin and mineral mixtures were American Institute of Nutrition vitamin mixture 76 and mineral mixture 76, respectively. Fiber was Celufil (US Biochemical, Cleveland, OH). Sucrose diet comprised 0.763 kcal/g protein, 2.677 kcal/g carbohydrate, and 0.45 kcal/g fat. Fat diet comprised 1.183 kcal/g protein, 0.194 kcal/g carbohydrate, and 4.647 kcal/g fat.

After 3 weeks animals presented clear preferences

Table 2. *Profiles of preference for each group*

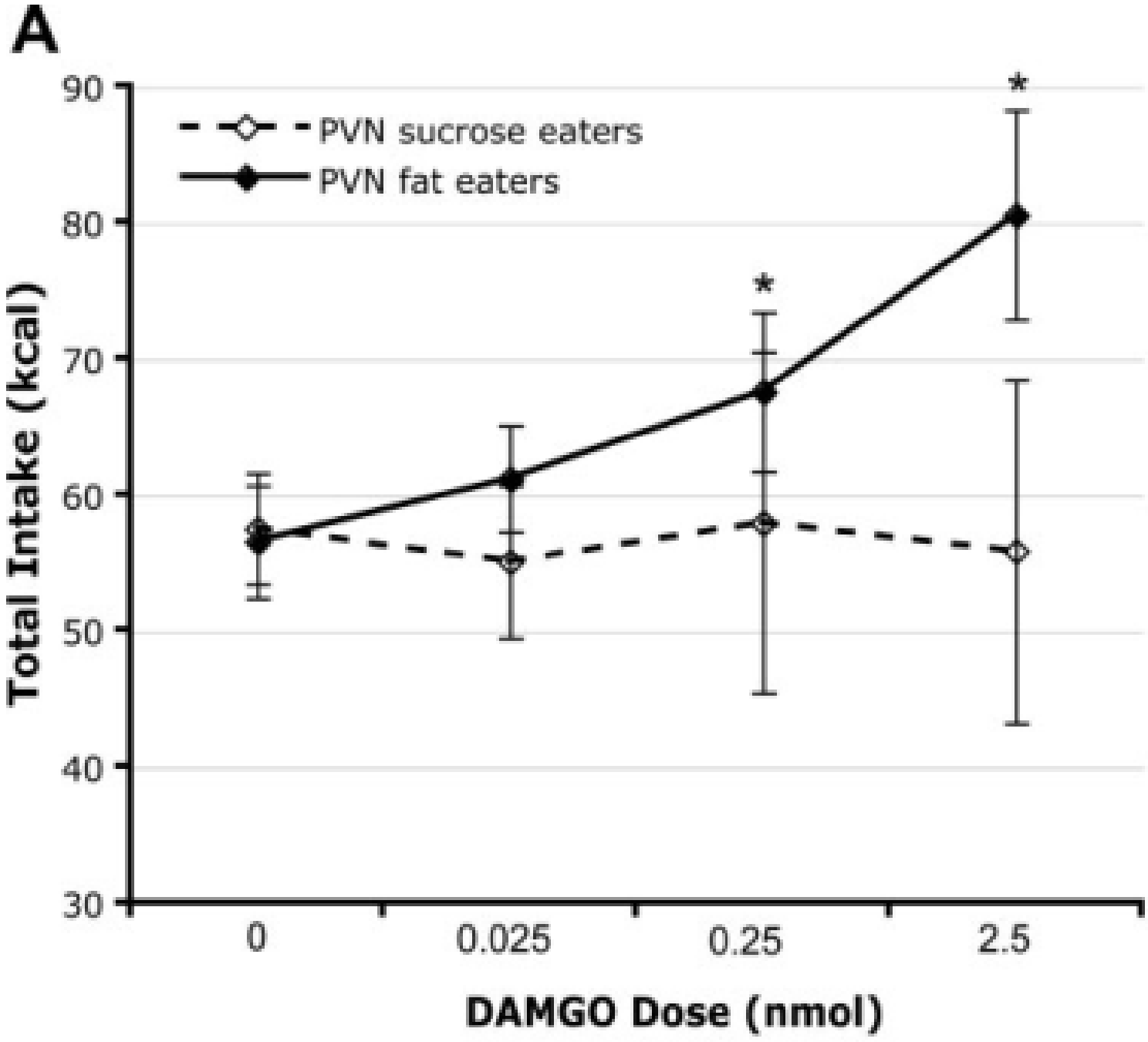
Preference Group	No. Rats	Fat-to-Sucrose	Favorite-to-Total	Total Intake
Fat	11	3.62±3.00	0.74±0.11	56.5±13.88
Sucrose	6	0.45±0.25	0.71±0.12	57.4±9.98

Preference ratios for experimental groups were determined on the last 3 days of the 10-day diet exposure. All values are calculated from kilocalories (±SD). Because fat-to-sucrose ratios are difficult to interpret, favorite:total ratios are also provided. Both groups consumed between 71 and 74% of their calories from their preferred nutrient and ate similar amounts of total calories.

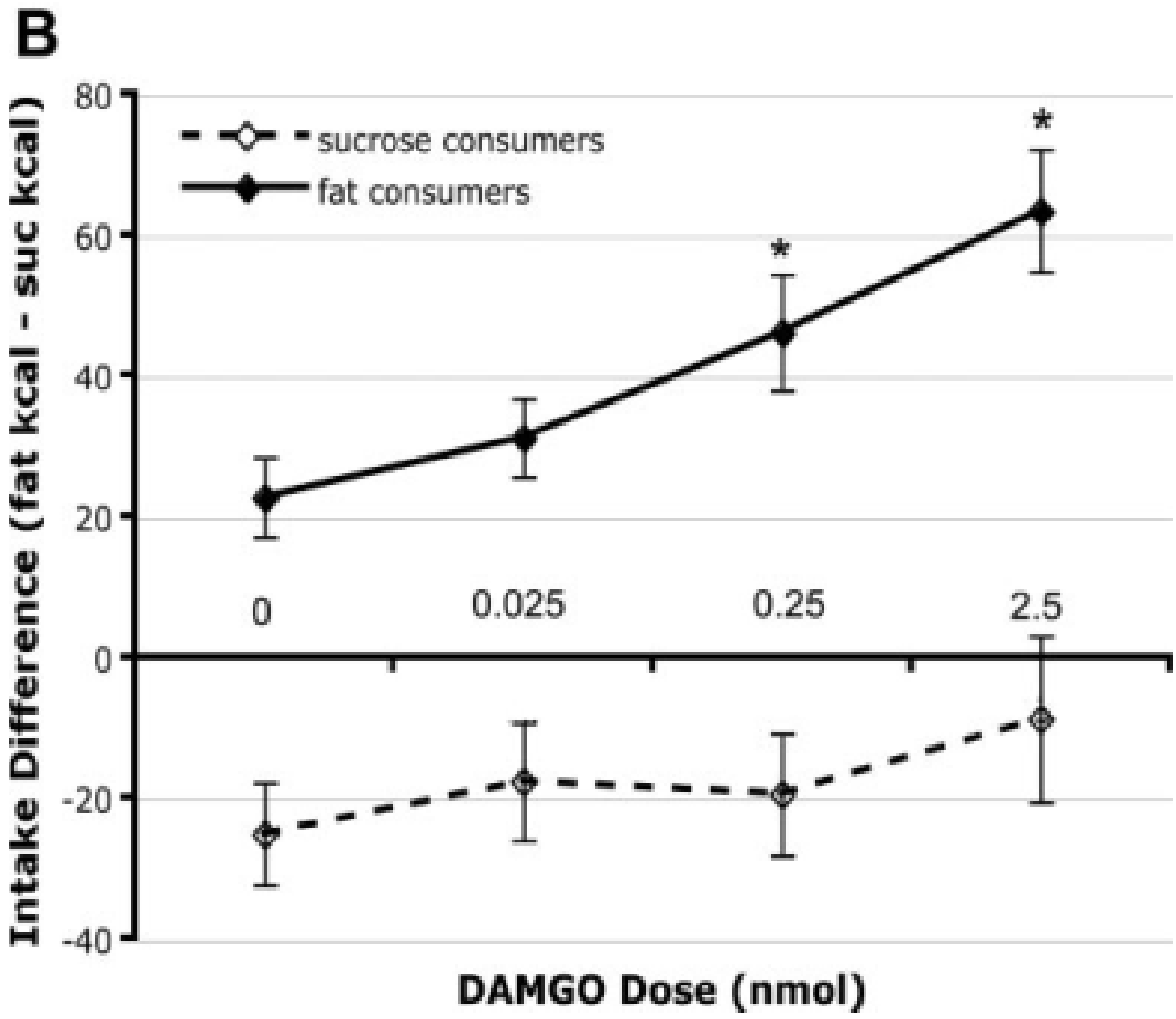
After 3 weeks animals presented clear preferences

- $\frac{\textit{fat intake}}{\textit{sucrose intake}}$
- If the ratio was >1 = fat consumer
- If the ratio was <1 = sucrose consumer

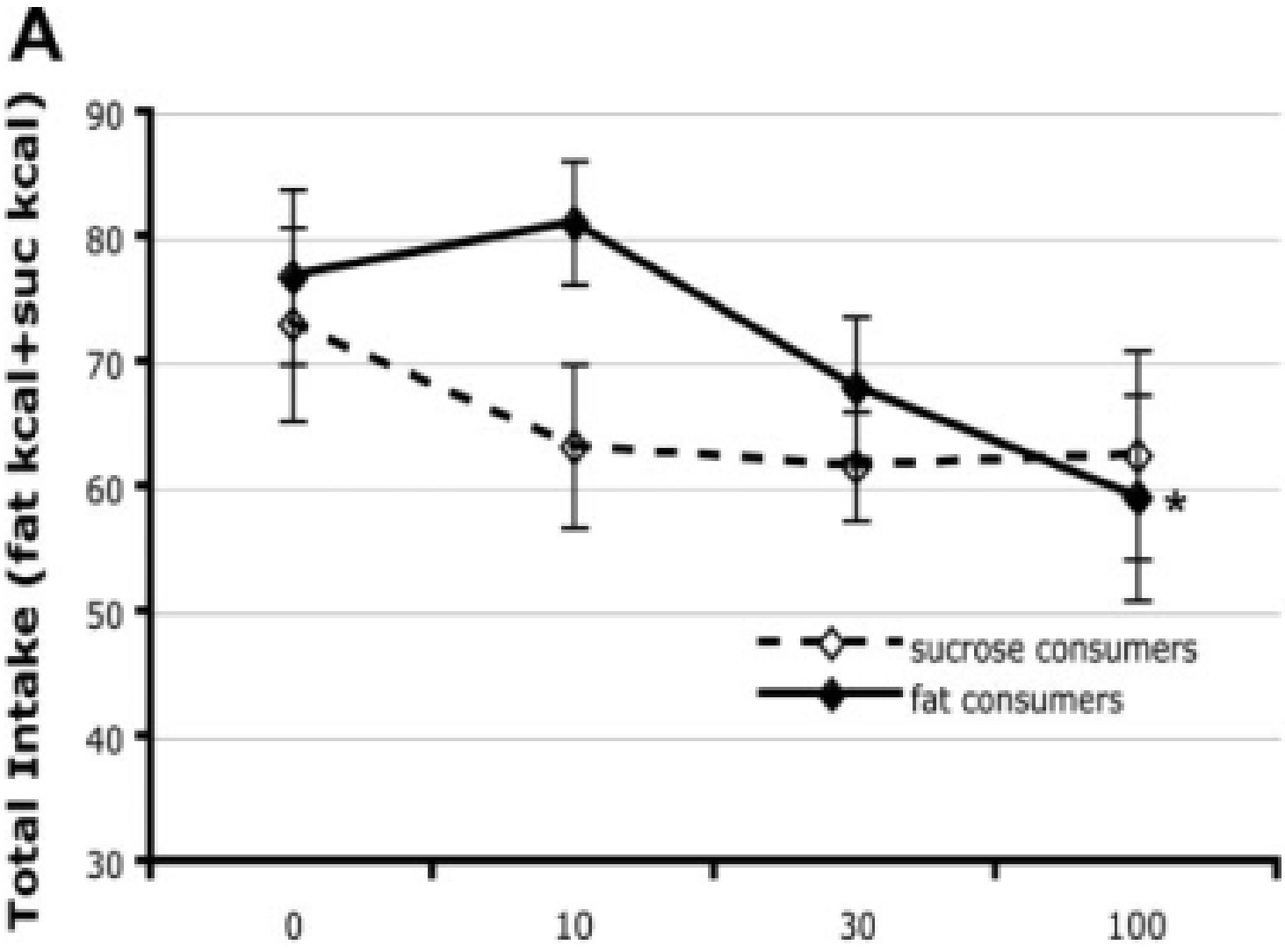
Total intake increased with DAMGO injection



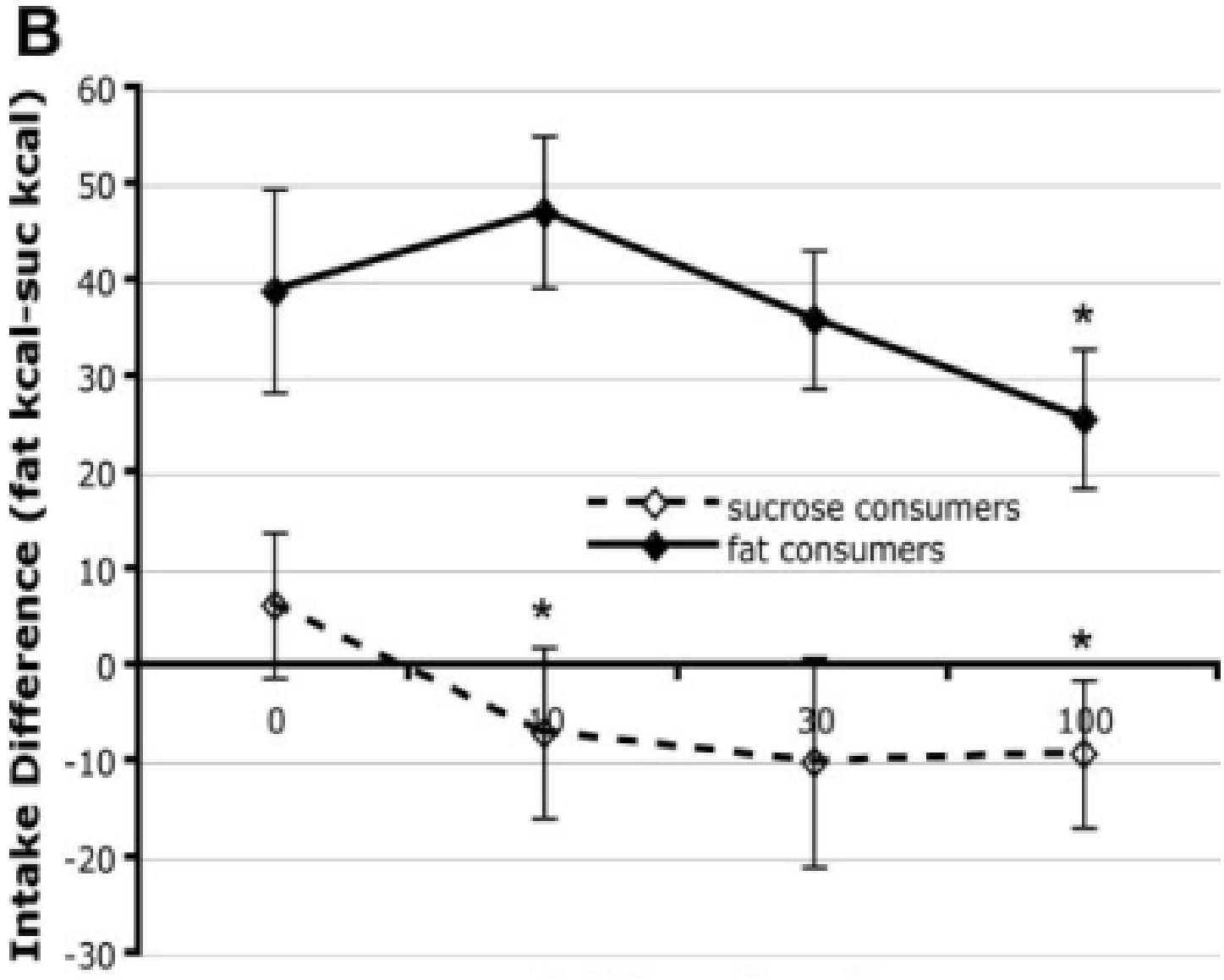
Intake difference increased only for fat preference group



NTX reduced total intake only for fat preference group



NTX reduced intake difference for both groups



The experimental setup (no-choice experiment)

- group 1: only sucrose diet
  - Exposed to sucrose
- group 2: food restricted to 80% of free-feeding intake
  - chow intake

The experimental setup (no-choice experiment)

- Injected with NTX intro the PVN
- Injected with NTX subcutaneously

Results (no-choice experiment) group 1

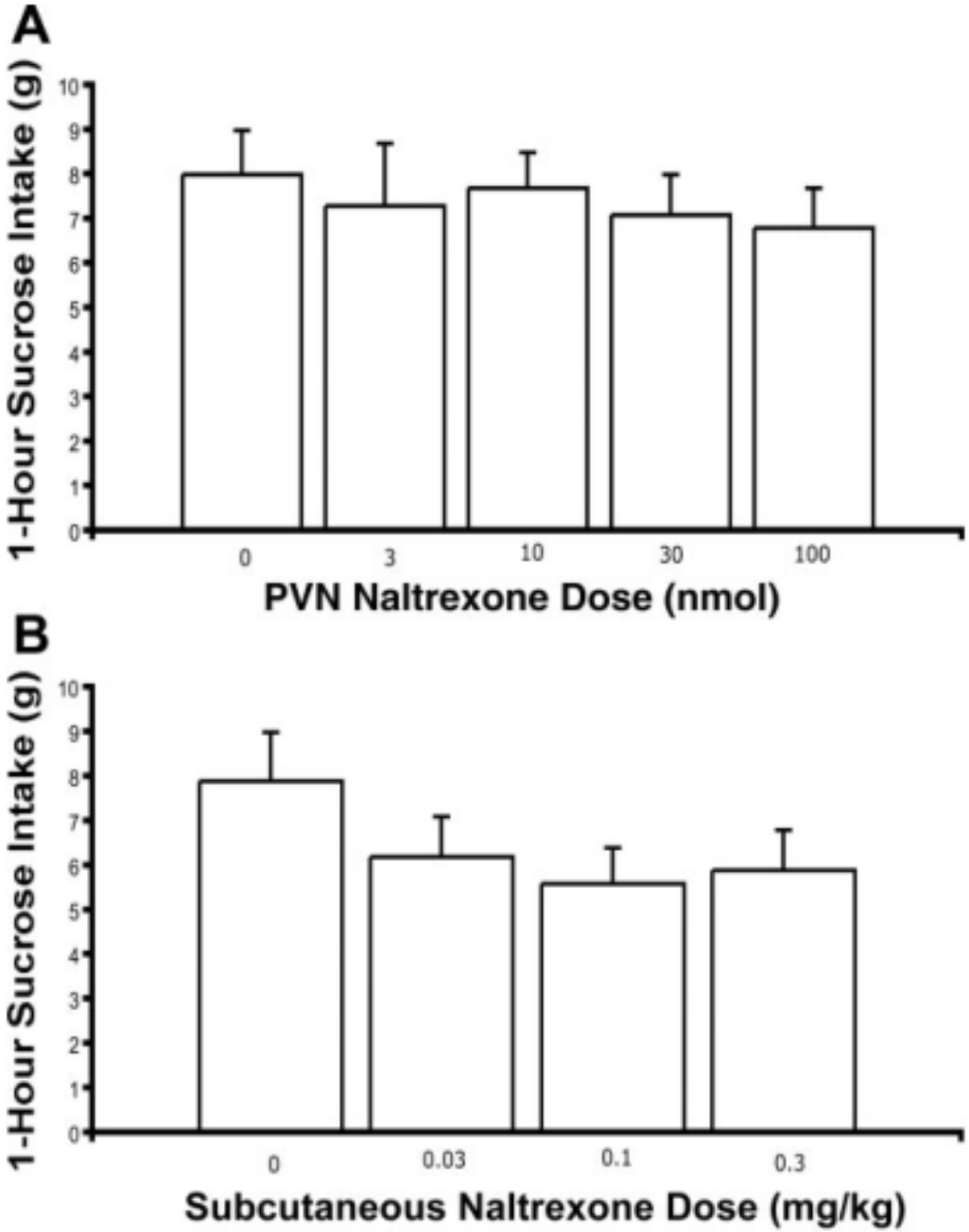


Fig. 4. Intra-PVN naltrexone (NTX) does not decrease spontaneous sucrose

Results (no-choice experiment) group 2

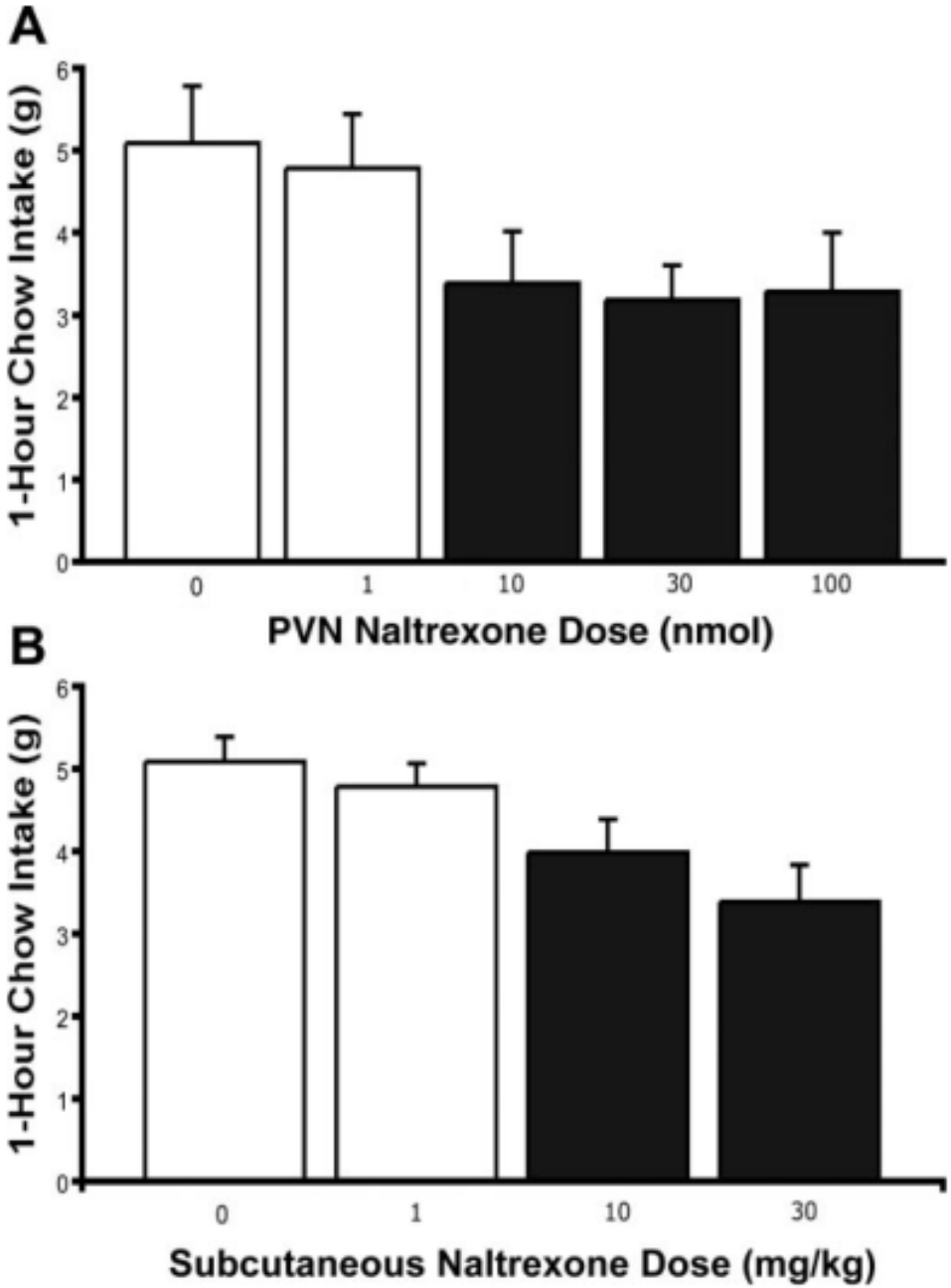


Fig. 5. Intra-PVN (*A*) and subcutaneous (*B*) NTX significantly inhibited 24-h

Contrary to author's hypothesis DAMGO and NTX effects were modulated by diet preference

- DAMGO stimulated fat intake primarily in fat preference group
  - opioid system is different in fat-preferring animals
  - opioids do not alter sucrose intake

The differential effects of DAMGO and NTX in fat and sucrose diet groups reveal differences in the opioid system

- NTX decreased the amount of fat-to-sucrose in both groups
  - NTX is a non-selective opioid antagonist
- however, DAMGO didn't increase fat-to-sucrose intake in sucrose group
  - DAMGO has high mu-receptor affinity
- if receptor ratios (mu-receptor to other types of receptors) were equal in both groups, no difference should be expected
  - fat group mu-receptors $>$ sucrose group mu-receptors
  - NTX blockade of non-mu-receptors is responsible for reduce fat intake in sucrose group

The differential effects of DAMGO and NTX in fat and sucrose diet groups reveal differences in the opioid system

- intra-PVN versus subcutaneous NTX injection tell us that sucrose intake regulation control-locus is somewhere outside the PVN ($p = 0.056$)
- so up until now, results indicate that PVN regulated fat intake and sucrose intake is regulated somwhere else
  - however if we include the chow-restriction experiment, we can add that PVN controls intake based on caloric need
  - so we could have a multi-function control locus or, as author's put it, results can be interpreted as PVN being a energy-control system because fat is the most calorie-dense nutrient

General discussion

- opioids may have differences in function depending on site of action
- opioid receptor activation effect is dependent on dietary preference
- PVN controls intake in time of caloric need (but fat-intake doesn't clearly fit in)

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