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Competing financial interests: declared. (Several of the authors consult with, and have received financial support from, companies and institutions, including pharmaceutical firms, that may have active programmes relating to PYY_{3–36}, of which we are not aware. Several of these companies have obesity-treatment development programmes and may therefore, from some perspectives, be considered competitors to companies pursuing PYY_{3–36}.)

Batterham et al. reply — The results of Tschöp *et al.*¹ on the lack of effect of peripheral administration of PYY_{3–36} on food intake in rodents are at odds with both the published literature^{2–8} (our Table 1) and with earlier data generated by the Tschöp laboratory.

It has been shown that PYY_{3–36} does not inhibit food intake in animals whose appetite is reduced by stress⁵ and this seems the likeliest explanation for the different findings now reported by Tschöp *et al.* The results of Tschöp *et al.* may also be undermined by their failure to measure the blood concentrations of PYY_{3–36} that were achieved following peripheral administration. Were they sufficient to result in inhibition of food

intake? In addition, their meta-analysis does not include earlier data generated in Tschöp's laboratory that confirm our findings⁹ (M.T., personal communication; data available from S.R.B. on request).

Tschöp *et al.* do not challenge the large body of appropriate mechanistic data that includes the inhibitory effect on food intake of intra-arcuate Y2-receptor (Y2R) agonists or PYY_{3–36}, changes in hypothalamic neuropeptide messenger RNA, the analysis of rodent hypothalamic explants and studies in Y2R-knockout mice^{4,9}. The human studies showing that PYY_{3–36} inhibits food intake^{9,10} are also uncontested.

Peripherally administered PYY_{3–36} inhibits food intake in procedure-acclimatized

Table 1 Summary of literature data on PYY_{3–36} and food intake in rodents

Species	Route	Study	Dose	Total number of animals (controls)	Effect
Wistar rats (male)	i.p.	Acute (freely feeding) ⁶	300 µg kg ⁻¹	28 (14)	Reduction in 24-h food intake*
	i.p.	Acute (dark phase) ⁹	3, 10, 30 µg kg ⁻¹	32 (8)	Reduction in 4-h food intake*
	i.p.	Acute (fasted) ⁹	3, 10, 30 µg kg ⁻¹	32 (8)	Reduction in 4-h food intake*
	i.p.	Acute (fasted) ⁹	50 µg kg ⁻¹	24 (12)	Reduction in 24-h food intake**
	i.p.	Chronic (7 d) ⁹	50 µg kg ⁻¹ d ⁻¹ (twice daily)	24 (12)	Reduction in food intake and body-weight gain**
	Intra-arcuate	Acute (fasted) ⁹	0.001, 0.01, 0.1 nmol	32 (8)	Reduction in 2-h food intake*
Diabetic Fatty Zucker rats (male)	Alzet pump	Chronic (28 d) ⁷	30, 100, 300 µg d ⁻¹	44 (14)	Reduction in cumulative food intake at highest two doses** Reduction in HbA1c and fructosamine*
Fatty Zucker obese non-diabetic rats (male)	Alzet pump	Chronic (56 d) ⁷	100 µg kg ⁻¹ d ⁻¹	20 (13)	Reduction in cumulative food intake and body weight*
129/J mice (male)	i.p.	Acute (fasted) ⁴	100 µg kg ⁻¹	16 (8)	Food intake reduction at 6 h*** and 24 h**
	i.p.	Acute (dark phase) ⁴	100 µg kg ⁻¹	16 (8)	Tendency to reduce 24-h food intake (NS)
	i.p.	Acute (freely feeding) ⁴	100 µg kg ⁻¹	20 (10)	Increased POMC mRNA at 6 h** and 24 h** Decreased NPY mRNA at 6 h**
POMC KO mice (male) and WT controls (male)	i.p.	Acute (fasted) ³	100 µg kg ⁻¹	64 (32)	Reduction in 4-h food intake**
	i.p.	Chronic (7 d) ³	100 µg kg ⁻¹ (twice daily)	32 (16)	No effect on food intake or body weight
NIH/Swiss non-obese mice (female)	i.p.	Acute (fasted) ⁷	0.1, 1, 3, 10, 30, 100, 300, 1,000 µg kg ⁻¹	192 (40)	Reduction in 1-h food intake with all doses greater than 3 µg kg ⁻¹ *
Ob/Ob ^{-/-} mice (female)	Alzet pump	Chronic (28 d) ⁷	100, 300, 1,000 µg kg ⁻¹ d ⁻¹	32 (8)	300 and 1,000 µg kg ⁻¹ d ⁻¹ doses led to reduction in cumulative food intake** and reduction in body-weight gain***
C57BL6/J DIO mice (male)	Alzet pump	Chronic (28 d) ⁷	30, 100, 300, 1,000 µg kg ⁻¹	76 (20)	Dose-dependent reduction in cumulative food intake*, body weight*** and reduced adiposity*
C57BL6/J mice (male) ⁵	i.p.	Acute (fasted) unacclimatized ⁵	3, 30, 100 µg kg ⁻¹	20 (5)	No effect on food intake in unacclimatized mice
	i.p.	Acute (fasted) ⁵	3, 30, 100 µg kg ⁻¹	20 (5)	Reduction in 4-h food intake*
	i.p.	Acute (fasted) ⁵	3, 100 µg kg ⁻¹	19 (10)	Reduction in 4-h food intake*
	i.p.	Acute (fasted) ⁵	30, 100 µg kg ⁻¹	19 (10)	Reduction in 4-h food intake*
Y2 receptor KO mice (males) and WT controls (males)	i.p.	Acute (fasted) ⁹	50 µg kg ⁻¹	40 (10)	Reduction of food intake in WT mice * No effect in Y2R KO mice
Ddy mice (male)	i.p.	Acute (fasted) ²	3 nmol	18 (9)	Reduction in 24-h food intake*
	i.p.	Acute (dark phase) ²	3 nmol	16 (8)	Reduction in 24-h food intake*
MC4R KO mice (male) and WT controls (male)	i.p.	Acute (dark phase) ⁵	3, 30, 100 µg kg ⁻¹	70 (36)	Reduction in 4-h food intake
Agouti mice (male) and WT controls (male)	i.p.	Acute (fasted) ⁸	0.02 µmol kg ⁻¹	44 (21)	Reduction in 2-h re-feeding***

Abbreviations: KO, knockout; NS, non-significant; i.p., intraperitoneal; WT, wild type; POMC, pro-opiomelanocortin; MC4R, melanocortin-4-receptor. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

rodents⁹, and these findings have since been supported by others²⁻⁸. Published studies confirming this effect (see our Table 1) are more extensive than the data presented by Tschöp *et al.* in their Table 1. PYY₃₋₃₆ reproducibly inhibits food intake in mice after an overnight fast and during dark-phase feeding in a dose-dependent manner²⁻⁸, but food intake in rodents is also inhibited by stress⁵.

Although Tschöp *et al.* claim that they performed assays to exclude stress, how can these be done in an ongoing feeding study? For example, the assessment of *c-fos* by immunohistochemistry necessitates killing the animal. Moreover, Tschöp *et al.* did demonstrate anorectic effects of PYY₃₋₃₆ when using non-stressful methods, such as infusion of the peptide with a minipump. They show in their Table 1 that food intake was reduced for three days in both C57BL/6 and *Ob/Ob*^{-/-} mice when using this non-stressful route of administration.

Contrary to their claims to have repeated our original studies, Tschöp *et al.* do not present data examining the effects of administering PYY₃₋₃₆ to mice given food after fasting. After feeding, endogenous PYY₃₋₃₆ is already raised and administration of exogenous PYY₃₋₃₆ is not effective. Many of the para-

digms listed in their Table 1 are not relevant because the administration of PYY₃₋₃₆ was either intracerebroventricular (when PYY₃₋₃₆ stimulates food intake through the NPY Y1/5 receptor) or to satiated animals.

We question the results presented in Fig. 1c of Tschöp *et al.* The data seem to be derived from two separate experiments that have been recombined. In those two experiments, there is no direct comparison between PYY₃₋₃₆ and CCK — the first compares CCK with PYY₁₋₃₆ and the second compares PYY₃₋₃₆ with other peptides (see their website www.pyyobesity.com).

Tschöp *et al.* question the potential of PYY₃₋₃₆ as a treatment for obesity. However, Pittner *et al.*⁷ have demonstrated that PYY₃₋₃₆ reduces food intake, decreases adiposity and improves glycaemic indices in several rodent models of obesity (see our Table 1).

This exchange exemplifies the fact that feeding is a behaviour and is thus very sensitive to the environment in which it is studied. Stress-inhibited food intake is a particularly poor circumstance in which to try to study another feeding inhibitor.

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