The modern world faces an exploding obesity epidemic, and despite many years of intensive research, the current clinically available nonsurgical treatment strategies are rather unsuccessful and drugs that were expected to alleviate the obesity problem had to be withdrawn from the market. Hence, understanding the physiological controls of eating has never been more important; this understanding may potentially help to develop effective pharmacological tools that reduce eating and eventually body weight without unacceptable side effects. Obesity research has to a large extent been focused on central nervous system neurotransmitters and also on long-term adiposity signals; the controls of individual meals were less in that focus, but it is now recognized that adiposity signals influence eating by modulating the effect of meal size controls (e.g. Refs. 1 and 2). The effects of adiposity signals and meal size controls appear to exhibit sex differences, and at least in females, estradiol appears to be the major factor that is involved in the control of eating, mainly by modulating meal size controls (3–6).

Basic research on the estrogenic inhibition of eating is of great health relevance. This research is expected to promote our understanding of disordered control of meal size in human eating disorders; women seem to be disproportionately more vulnerable to these disorders than men (7–9). These disorders include anorexia nervosa, bulimia nervosa, and binge-eating disorder, which is an important contributor to obesity. Further, morbid obesity is more prevalent in women than men (10).

Estradiol has been shown to control eating and body weight mainly via modulating the potency of feedback signals that control meal size (5, 6). The best investigated interaction is that between cholecystokinin (CCK) and estradiol; the data indicate that estradiol increases the satiating potency of exogenous and endogenous CCK (11–13). Similar mechanisms may be operational for glucagon because the effects of glucagon and of glucagon antibodies to decrease or increase meal size, respectively, were both amplified by estradiol in ovariectomized (OVX) rats (14). Finally, our own unpublished data indicate that estradiol enhanced the acute eating inhibitory effect of exogenous amylin in OVX rats (Asarian L., N. Geary, and T. Lutz, unpublished observations).

It is a well-established phenomenon that the absence of estradiol leads to a temporary increase in eating and a sustained increase in body weight (5, 9, 11). This phenomenon is of clinical relevance because estradiol levels decrease in postmenopausal women; importantly, postmenopausal women make up a high percentage of the obese population.

Because most nonsurgical treatment options for obese people have been withdrawn from the market due to unacceptable side effects, the amylin-based combination therapy with leptin has raised increased interest as an effective antiobesity treatment. The recent paper by Trevaskis et al. (15) provides new and to a large extent surprising insight into the role of estradiol in the control of eating, in particular in terms of estradiol’s interaction with chronic amylin treatment. Trevaskis et al. used diet-induced obese (DIO) female rats that were OVX; part of the OVX rats received cyclic estradiol replacement that mimics the physiology of an intact female sexual cycle (16). Several key findings reported in this paper are worth mentioning here. Similar to previous studies in intact male DIO rats (17; see also Ref. 18), amylin reduced the body weight gain in sexually intact female sham-operated DIO rats. The effect was similar in OVX rats that received physiological estradiol replacement therapy; interestingly, amy-
In OVX rats that had not received estradiol replacement treatment. In other words, the absence of estradiol appeared to enhance amylin action. In fact, in OVX rats without estradiol replacement, amylin resulted in a decrease in body weight below the baseline levels after a 4-wk infusion period, whereas all other rats gained weight. The vehicle-corrected weight loss in OVX rats that did not receive estradiol replacement was about 11%; this was double that observed in the other two groups of rats. Amylin’s effect to specifically reduce body adiposity was slightly (but not significantly) more pronounced in OVX rats that did not receive estradiol replacement compared with the other groups of animals.

Trevaskis et al. (15) also found that amylin’s effect on body weight was at least in part due to reduced eating. The latter effect was slightly (but not significantly) stronger in OVX rats without estradiol replacement than in the other groups of rats. As mentioned, previous studies had shown that estradiol’s effect on eating seems to be mainly due to a modulation of the effect of satiating hormones like CCK (11–13). This may explain why the overall reported effects of estradiol on eating are due to a decrease in meal size, whereas the meal number is actually increased. However, the latter effect typically does not compensate for decreased meal size (5, 6, 9). Whether the influence of (lack) of estradiol on amylin’s eating inhibitory effect was also due to a meal size effect has not been studied in the paper by Trevaskis et al.

As expected, energy expenditure in OVX rats was lower than in sham-operated control animals (19; but see Ref. 20); this effect was partly restored by amylin treatment. Furthermore, energy expenditure in amylin-treated OVX rats was similar to that of vehicle treated controls but higher than in a second control group that was pair fed to amylin treated rats. Overall, and similar to previous studies (21), the results suggest that amylin maintained energy expenditure at a higher level than that of control rats despite the amylin-induced reduction in body weight. Based on recent promising findings about the clinically relevant pharmacological interaction between amylin and leptin (22–24), Trevaskis et al. (15) also tested whether the enhanced body weight-lowering effect of amylin in OVX rats required intact leptin signaling. However, the data presented in the paper by Trevaskis et al. (15) suggest that this was actually not the case.

Several mechanistic aspects of the interaction between estradiol and amylin remain unresolved. It remains generally unknown where this interaction might take place, but a central nervous system site seems most plausible. It is well established that amylin’s effect on eating is mediated by the area postrema (AP) (25–27), and estradiol’s effect on eating and in particular its effect on meal size controls also seems to be a hindbrain effect (4–6, 12, 13). Trevaskis et al. (15) found no difference in the primary activation of AP neurons between OVX and sham operated rats after amylin, at least when assessed by c-Fos immunoreactivity. It is, however, important to realize that c-Fos activation does not necessarily directly reflect the behavioral effects of amylin (28), so that at present it should not be excluded that estradiol and amylin may interact via the AP. In fact, the paper by Trevaskis et al. does give a hint that the AP may be involved. They report that OVX rats exhibited decreased neurogenesis in the AP, as assessed by 5-bromo-2’-deoxyuridine immunoreactivity. This effect was completely restored by amylin. Whether restored neurogenesis would result in an increase in the number of functional amylin receptors and hence an increase in amylin sensitivity is unclear but seems to be a plausible explanation. Amylin’s effect on neurogenesis does not seem to be isolated to the AP because decreased neurogenesis in the hippocampus in OVX rats, which served as positive control area (29, 30) was also restored by amylin (15).

The overall conclusion of the study was that amylin seems to exert greater body weight-lowering effects in rats with low estradiol levels; hence, the present study may serve as an important pilot study about the use of amylin or its agonists in the treatment of obesity in particular in postmenopausal women, a group of patients that is over-represented in the obese population.

From a more principal point of view, it is important to realize that the present study yields interesting pharmacological results but does not test the question whether the interactions between (lack of) estradiol and amylin are physiologically relevant. Because preliminary data indicate that the acute eating inhibitory effect of amylin may be enhanced by estradiol in OVX rats (Asarian L., N. Geary, and L. Lutz; unpublished observation), this question deserves further study that must include different experimental conditions. Nonetheless, and given the paucity of other nonsurgical treatment options, especially since the withdrawal of sibutramine and rimonabant from the market, amylin-based pharmacotherapy seems to constitute a viable alternative to treat obesity that clearly deserves further study.

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