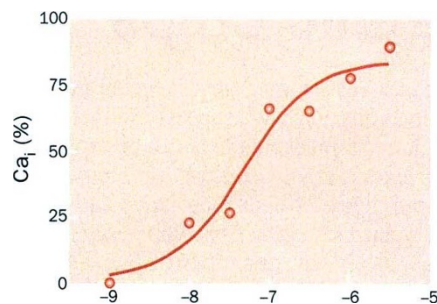


Neural control of dieting

SIR — Tecott *et al.*¹ have shown that transgenic mice lacking the receptor for the 5-hydroxytryptamine neurotransmitter subtype 5-HT_{2C} become obese through overeating, indicating a primary role for this receptor in the satiety response; these animals do not respond to the 5-HT_{2C} receptor agonist *m*-chlorophenylpiperazine (mCPP). Cowen *et al.*² emphasized that antagonists for this receptor, such as clozapine and mianserin, cause troublesome weight-gain in people; clozapine abolishes the endocrine responses to mCPP in humans³. These authors showed that dieting may be difficult because of an imbalance of brain 5-HT release and 5-HT_{2C} receptors: dieting lowers plasma tryptophan, the precursor for brain 5-HT, which lowers levels of this neurotransmitter in the brain, but secondarily increases postsynaptic 5-HT_{2C} receptor sensitivity². Cowen *et al.* showed an increase in 5-HT_{2C} receptor sensitivity by administering mCPP to women undergoing a 1,000-kcal daily diet; they observed a marked increase in the prolactin response among those who dieted, and suggested that lowered 5-HT levels cause receptor supersensitivity.

Dexfenfluramine is a widely prescribed dieting agent; it has been shown to be effective in causing weight loss⁴, although the mechanism has not been fully defined. Dexfenfluramine causes a marked release of 5-HT from neurons by inhibiting uptake of this neurotransmitter and by direct release⁵. In this way, the drug will counteract the effects of reduced tryptophan levels. However, dexfenfluramine has negligible affinity for 5-HT receptors. The principal metabolite of dexfenfluramine, (+)norfenfluramine, is a potent ligand in displacing [³H]-mesulergine binding to human recombinant 5-HT_{2C} receptors transfected into cultured CHO cells, with a *K*_i of 1.6 ± 0.3 μM (*n*_{Hill}, 0.8 ± 0.1; dexfenfluramine *K*_i, 16.4 ± 3.3 μM; *n*_{Hill}, 1.0 ± 0.2), confirming previous binding experiments in neuronal tissue⁵. Brain levels of (+)norfenfluramine in rats given dexfenfluramine at an appropriate anorectic dose (1.3 mg per kg intraperitoneally) are of the order of 3.6 nmol per g (ref. 6), several times the threshold for receptor occupation. We also show that (+)norfenfluramine is an agonist at 5-HT_{2C} receptors, as (+)norfenfluramine



Cytosolic calcium levels in CHO cells transfected with the human recombinant 5-HT_{2C} receptor. The concentration–response curve for (+)norfenfluramine for increase in intracellular calcium is expressed as a percentage of the final response to 5-HT (3 μM).

(0.1–10 μM) increases calcium levels in the transfected CHO cells (see figure); this effect is blocked by the mixed 5-HT_{2A}/5-HT_{2C} receptor antagonist mesulergine (100 nM). The 5-HT_{2C} agonist (–)-2,5-dimethoxy-4-iodoamphetamine (3 μM) mimics the effects of (+)norfenfluramine by increasing intracellular calcium in CHO cells transfected with the 5-HT_{2C} receptor. Thus, dexfenfluramine shows a unique pharmacological spectrum by releasing brain 5-HT, which will also prevent 5-HT_{2C} receptor

supersensitivity, and also by acting, via its principal metabolite (+)norfenfluramine, as an agonist at 5-HT_{2C} receptors and thereby directly inducing satiety. The effects of dexfenfluramine as an anorectic agent in humans are abolished by the co-administration of ritanserin⁷.

These findings emphasize the role of 5-HT_{2C} receptors in controlling food intake and satiety, and suggest that dexfenfluramine might reset the balance between 5-HT release and 5-HT_{2C} receptor stimulation. Further work is required to define how control of this receptor system parallels other, recently described, systems such as glucagon-like peptide-1 (ref. 8) and leptin^{9,10}, to modulate satiety and obesity. In this respect, both the leptin receptor and 5-HT_{2C} receptors are highly expressed in the choroid plexus and, to a lesser extent, the hypothalamus.

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Counting species names

SIR — Many estimates of global biodiversity depend critically on the extent to which species have been catalogued^{1–3}. Estimating the number of recorded species is not straightforward, because an unknown fraction of published descriptions refers to previously named species^{1,4}. It has recently been proposed that the overall fraction of synonyms can be estimated from extrapolations of revisions of particular groups⁵. However, the statistics involved are tricky, and it is unclear whether the groups used to estimate ‘synonymy rates’ are representative¹.

The point can be illustrated with three groups of molluscs from the Mediterranean region. Melanopsids are relatively large, conspicuous freshwater snails. In this century, the number of species accepted by different workers has progressively diminished from more than 100 to only one, extremely variable, exceedingly ancient ‘species’⁵. Thus, the estimated synonymy rate in this group ranges from 0 to more than 99%. Comparative anatomy and molecular genetics unequivocally show that the number of species is indeed fairly large⁶. A taxonomic revision in progress indicates that the amount of synonyms is probably near 40%.

Freshwater mussels (unionoids) have a similar taxonomic history. Many species

were described using criteria that few, if any, contemporary biologists would agree upon. These names were progressively lumped into only seven quite variable ‘species’ (excluding those living in the Nile), resulting in huge lists of synonyms. However, there is now strong and growing evidence that this group has undergone a remarkable diversification in the area⁷; even so, this upwards revision has only a slight impact on the synonymy rate, which drops from 99 to 93%.

A very different situation occurs in hydrobiids, minute snails often living in springs and subterranean waters. Their small size and the general absence of conspicuous characters on their shells have kept them away from taxonomists. But most of the 50 species described in Iberia⁸ represent valid species, and indeed there

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