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Where now for obesity research?

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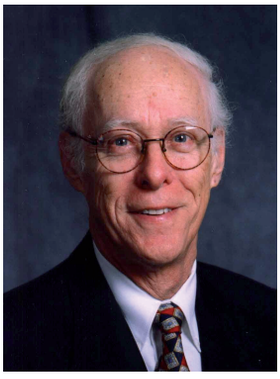

"The challenges are to find those mechanisms that will produce clinically significant weight loss, provide durable responses and be free of significant side effects."

As three new applications for pharmacotherapy were submitted to the US FDA for review and approval, 2010 began with hope that the findings from obesity research would translate into new therapies for obese patients [1–3]. During the year, there were actually five Advisory Panels to evaluate proposed drug or drug combinations for the treatment of obesity and review of one older drug where an outcome trial had suggested an increased risk [4] along with a panel to review an expanded indication for surgical treatment with the lap-band. The results of three panels were negative, with the External Advisory Committees voting against approval of one new drug and one combination treatment using older drugs and no longer favoring marketing of an existing drug. A ray of hope appeared when the final two panels voted to approve a second combination of two older drugs for treatment of obesity and the expanded use of the lap-band at a lower BMI in higher risk obese individuals.

Thus, in spite of years of research, only a single drug has been approved by the FDA for long-term use [5]. By contrast, there are many drugs acting through one of several different mechanisms to treat hypertension, atherosclerosis and diabetes. Why have scientists doing obesity research not been as successful as scientists in these other diseases areas in identifying successful drugs?

Drugs to treat obesity can work on structures in the brain, for example, amphetamine, fenfluramine or serotonin [6]. Alternatively, they can work outside the brain by blocking intestinal digestion or as hormonal agents acting on gastrointestinal receptors that can inhibit feeding.

One difficulty is that drugs that reduce food intake by acting on brain receptors may also act on other receptors to produce unwanted side effects, such as alterations in mood or other behaviors. These undesirable, and often unintended, side effects from drugs sounded the death knell for pheylpropanolamine [7], an α-1 adrenergic antagonist that reduces food intake and produces modest weight loss, but is also a vasoconstrictor that can raise blood pressure. In a case-controlled study of strokes, younger women using phenylpropanolmine appeared to be at increased risk for stroke and phenylpropanolamine was subsequently taken off the market by the FDA [7].

Addiction is another problem associated with some centrally acting sympathomimetic drugs. Shortly after amphetamine was shown to reduce body weight, it was also shown to produce addiction. This probably reflects the fact that it hits two targets, one of which, the norepinephrine receptor, is beneficial and reduces food intake and the other, the dopamine receptor, is harmful and can produce addiction.

Drugs reducing food intake by acting on serotonin receptors have also experienced problems. Fenfluramine has a β-phenethylamine structure like amphetamine, but, in contrast to amphetamine, acts almost exclusively on serotonin receptors. Fenfluramine was approved by the FDA in 1975 to treat obesity. In 1997, patients treated with fenfluramine and phentermine were reported to

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develop aortic regurgitation in up to 25% of the cases [8]. Based on these findings, fenfluramine and its dextro-isomer, D-fenfluramine, were removed from the market in September 1997. The effect on food intake was probably through action on serotonin-2C receptors, and the valvulopathy through effects on serotonin-1B receptors.

Another problem is that the primary target for a drug may also produce other unwanted effects. Canabinoid agonists stimulate food intake whereas antagonists to the cannabinoid receptors reduce food intake and body weight [9]. However, these same receptors are involved in emotional responses, and blocking these receptors produced feelings of dysphoria and increased suicidal ideation in some people.

Inhibition of the dopamine receptors is another example where food intake and behavior interface. Dopamine receptors are involved in the pleasurable or hedonic experiences related to eating and other activities. As already noted, activation of these receptors may also be involved in the addiction associated with amphetamines. This problem of dual action surfaced with ecopipam, a selective anatagonist to the dopamine D1/D5 receptor, which reduced food intake, but also produced increased suicidal ideation [10]. Clinical trials were stopped because of these unintended side effects.

Neuropeptide Y is a widely distributed peptide that acts on one of five receptors in the brain [5,6]. Activation of two of these NPY receptors, Y-1 or Y-5, dramatically increases food intake in animals, and continued stimulation of the NPY receptors produces obesity, making an antagonist to this receptor an attractive target for an anti-obesity drug. One such drug, MK-0557, is a highly selective NPY-5 receptor antagonist with 98% receptor occupancy at low doses [11]. After finding a suggestive dose–response to the drug, larger trials were initiated, and in a 52-week study, the drug-treated group lost 2.2 kg, which was significantly more than the 1.1 kg lost by placebo group. This small, but statistically significant, difference was not substantial enough for further drug development, but did demonstrate that the NPY-5 receptor was involved in modulating food intake and body weight in human beings.

Box 1. Potential drug mechanisms.

CNS mechanisms
- Norepinephrine
- Serotonin
- Dopamine
- γ-Aminobutyric acid
- Melancortin 3/4 receptors
- Neuropeptide Y receptors
- Agout-related polpepide
- Melanocyte-stimulating hormone
- β-endorphin
- Orein
- Melanin concentrating hormone
- Corticotrophin releasing hormone
- Cannabinoid receptors

Peripherally actin mechanisms
- Leptin
- Amylin
- Ghrelin ghrelin-*O*-acyl transferase (GOAT)
- Glucose-insulin peptide (GIP)
- Bombesin-related peptide
- Cholecystokinin
- Polypeptide Y
- Oxyntomodulin
- Adropin

The limited response to an agonist at the melanocortin-4 receptor is a second example of inadequate pharmacological response [12]. Based on animal and genetic studies, the melanocortin-4 receptor is thought to play an important role in the control of food intake [5,6]. MK-0493 is a selective and novel melanocortin-4 receptor agonist that has been evaluated clinically [12]. This drug produced a small, but not statistically significant weight loss, relative to baseline. These clinical studies suggest that a MC4R agonist alone may not be an easy clinical target, and one possible explanation for the poor effect is the redundancy that exists in the control of food intake.

Another challenge is the lack of a durable clinical effect. The antidepressant, fluoxetine, produces dose-related weight loss in overweight patients, but even as therapy is continued the effect wanes, suggesting that its use in obesity can only be short term [13]. Another mechanism for loss of clinical effect is the development of antibodies. Peptides are 'foreign' substances and would be expected to produce antibodies. Ciliary neurotrophic factor is a peptide that produces weight loss in animals by acting on hypothalamic receptors. When tested in human beings it also produced modest weight loss, but antibodies developed in up to 70% of those treated with this drug. The antibodies were the kind that blocked the effect of the drug, and development was terminated [14].

In contrast to the disappointing pattern of response to drugs acting in the CNS described above are some recent studies with drugs acting primarily outside the CNS. The glucagon-like peptide (GLP)-1 agonist, exenatide, which has been approved for treatment of diabetes, is derived from the desert Gila monster. This drug, without the use of diet or exercise, is consistently associated with weight losses of 3–5 kg, which lasts as long as the drug is continued [15]. Data from clinical studies on another GLP-1 agonist suggest similar benefits. Liraglutide is a synthetic modification of the natural GLP-1 peptide designed to reduce its rapid biological degradation. When this peptide is injected into obese individuals there is a dose-related loss of weight [16]. The duration of this weight loss has not been demonstrated yet, but clinical trials are underway. Both exenatide and liraglutide are approved for treating diabetes. In addition to this effect they have been suggested to have beneficial effects on the islet cells of the pancreas where insulin is made, as well as on the vascular system. Thus, the concerns that have been raised about the cardiovascular responses to drugs such as sibutramine [4], which raises blood pressure, do not appear to apply to liraglutide or exenatide.

Leptin and amylin are a pair of peptide drugs, one of which, leptin, is produced by fat cells, and the other, amylin, by the β-cell of the pancreas. They have been

found to act together to enhance weight loss. Amylin is currently approved to treat diabetes and has as one effect a reduction in food intake. In combination, leptin and amylin produce greater weight loss and reduction of food intake than the individual peptides alone [17].

Box 1 includes the mechanisms discussed and a number of others. At present there is no shortage of potential mechanisms for research workers to explore. The challenges are to find those mechanisms that will produce clinically significant weight loss, provide durable responses and be free of significant side effects. Drugs like the statin drugs for atherosclerosis or angiotensin–receptor agonists, that have been so effective for lower cardiovascular disease risk and hypertension, have yet to be identified for the treatment of obesity. Thus, the future for obesity research looks bright and challenging.

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