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Review article

Bench to bedside in appetite research: Lost in translation?

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ABSTRACT

Despite substantial progress in our understanding of the complex bio-machinery involved in the regulation of appetite and energy homeostasis, few weight loss drugs are currently government-approved in the USA or Europe. While acknowledging novel drug monotherapies (such as Belviq® & Saxenda®), this review focuses on the various drug polytherapies that are currently attracting so much research interest. Unfortunately, however, the dependent variables in these new studies remain firmly rooted in outcome measures i.e. reduced food intake and bodyweight. Such evidence is clearly essential, as are physiological data bearing upon potential 'off-target' effects of any new treatment. However, as emphasised by many authors, this profiling has to be matched by sophisticated behavioural analysis addressing fundamental 'process' questions such as how such reductions in intake and/or bodyweight have been achieved. The value of behavioural analysis is exemplified, and it is argued that such a process-led approach should optimise the translation from preclinical to clinical development of candidate drugs, and avoid yet further expensive blind alleys.

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1. Context: the obesity pandemic

Stroll down your high street, or simply observe folk in bus and rail stations, ferry terminals, airports, swimming pools and on beaches, and you cannot be fail to be disturbed by the sheer bulk of many of your fellow humans. Your observations will confirm two other facets of modern life; namely, that we are constantly bombarded with visual and olfactory enticements to consume cheap, energy-dense foods, preferably in 'large' portions, yet do not really have to exert ourselves in order to acquire such delights. For many of us, there is really only one possible outcome to this imbalance in the energy equation, i.e. weight gain.

Obesity, the excessive accumulation of body fat, is most frequently diagnosed using the body mass index or BMI (kg/m^2). People with a BMI ≥ 25 are considered overweight, while scores of 25.00–29.99, ≥ 30, 30.00–34.99, 35.00–39.99, and ≥ 40 define pre-obesity, obesity, and obesity classes I–III, respectively (Chugh

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and Sharma, 2012; Nuffer et al., 2016). It should be noted that there are potential differences in BMI definition as a function of ethnicity (National Obesity Observatory, 2011), and that more accurate indices of obesity exist (e.g. body composition analysis). With these caveats in mind, it is generally accepted that obesity has now reached pandemic proportions with some 1.9 billion adults overweight, more than 600 million adults obese, and over 40 million under-fives obese (WHO, 2015). Childhood and adolescent obesity is of particular concern in view of the serious long-term consequences for physical and mental health (Adair, 2008; Franks et al., 2010; Reilly and Kelly, 2011). Not only can early exposure to unhealthy eating habits lead to a greater risk of obesity in later life (Anzman et al., 2010), but the 'developmental origin hypothesis' (Volkow and O'Brien, 2007) holds that high-fat or high-sugar exposure in the womb can alter how brain and body develop in anticipation of future environments, including patterns of nutrient selection (e.g. Ong and Muhlhausler, 2011; Teegarden et al., 2009). More intriguingly still, recent research has suggested that rodent maternal obesity at conception can program brain reward circuitry in offspring by dramatically altering the expression of opioid peptides and their receptors (Grissom et al., 2014), while human paternal and grand-paternal obesity may influence metabolic function in future generations via epigenetic re-modelling of sperm DNA methylation (Cropley et al., 2016; Donkin et al., 2016). Other important recent developments, the full ramifications of which have yet to be appreciated, concern (i) the role played by gut microbiota in the regulation of bodyweight and metabolism (Cryan and Dinan, 2012; Ridaura et al., 2013), with growing evidence that emulsifiers in processed foods significantly contribute to low-grade intestinal inflammation, obesity and the metabolic syndrome (e.g. Chassaing et al., 2015), and (ii) the therapeutic potential of pharmacologically converting potentially harmful white adipose tissue (WAT; energy storage) into physiologically more beneficial brown adipose tissue (BAT; energy dissipation) (for recent review: Giordano et al., 2016).

The health consequences of obesity not only impose serious restrictions on quality of life, they can also be life-threatening. The obese experience day-to-day problems with osteoarthritis, back pain and mobility (Lean et al., 1998) as well as breathing difficulties caused by fat store-induced reductions in lung volume (Kopelman, 2007). Furthermore, obesity is a major risk factor in the development of chronic disorders such as type-2 diabetes, hypertension, heart disease and stroke, sleep apnea and certain cancers (Kissbeah et al., 1989), and can reduce life expectancy by up to 20 years (Fontaine et al., 2003). In addition to these health costs, obesity is associated with major economic costs (e.g. Speakman and O'Rahilly, 2012). In the U.K., the annual cost of obesity and its consequences has been estimated at around £3.5 billion, a figure that doubles when overweight patients are included in the calculation. As this spend approximates 2.5% of the annual National Health Service budget (House of Commons, 2004), the clinical need for safe and effective interventions is obvious.

2. Treatment options

Although prevention through early education and/or later retraining is a major goal, therapeutic interventions are essential for those who are currently significantly overweight or obese. Even modest reductions in bodyweight (e.g. 1-year weight loss of 5 kg) can have significant health benefits including improvements in insulin sensitivity, glycaemic control and blood pressure (e.g. Goldstein, 1992). Current treatment options comprise lifestyle change, surgery and pharmacology (for review: Wyatt, 2013). Although the focus of the present review is on pharmacotherapy, it is nevertheless appropriate to briefly comment upon the other approaches – particularly since lifestyle change and surgery are very relevant to current thinking about optimal drug treatment strategies.

Lifestyle modification, including dietetic, exercise and psychological interventions, are the cornerstones of successful weight management programmes. This strategy encourages a negative energy balance, whereby calories are restricted (i.e. dieting) and/or energy expenditure increased (i.e. exercise), and has repeatedly been shown to reduce obesity and associated risk factors (Brown et al., 2009; Wadden et al., 2005). However, by itself, lifestyle modification is usually effective only in the short- to medium-term, with most patients regaining lost weight over longer timeframes (Anderson et al., 2001). As such, medication is now normally recommended as an adjunct therapy alongside or following successful lifestyle intervention (e.g. Bray, 2013; Patel, 2015; Wadden et al., 2005, 2013). Bariatric surgery, such as Roux-en-Y bypass or gastric banding, is much more effective than non-surgical interventions for weight loss and diabetes remission (Gloy et al., 2013; Stefater et al., 2013), and is currently recommended for adults with Type 2 diabetes and a BMI $\geq$ 35 (National Institute for Health and Care Excellence, 2014). Although this approach is not without significant risk (e.g. perioperative death, anastomotic leak, infection, need for re-operation; e.g. Puzziferri et al., 2014), the impact of bariatric surgery on gut hormone release, and the importance of these biochemical alterations in promoting appetite suppression and weight loss, has instigated an exciting new era of anti-obesity drug development based on gut peptide combinations (see Section 4).

3. 'Magic bullets' in 20th century

Drug treatment for obesity generally falls into one of three (non-mutually exclusive) categories: appetite suppressants, inhibitors of fat absorption, and/or agents that increase energy expenditure and thermogenesis (Li and Cheung, 2009). However, as detailed in many recent reviews (e.g. Adan, 2013; Bray and Greenway, 2007; Colon-Gonzalez et al., 2013; Heal et al., 2012; Jones and Bloom, 2015; Krentz et al., 2016; Rodgers et al., 2012), the record of anti-obesity drug development since the beginning of the twentieth century (the search for so-called 'magic bullets') has for the most part been far from glorious. Many treatments have been tried, tested, government-approved and introduced to clinical practice, only to be subsequently withdrawn in the face of significant adverse ('off-target') effects. In brief, agents that succumbed to this rather ignominious fate during C20 include sheep thyroid extract (cardiovascular risk), dinitrophenol (potentially fatal hyperthermia), *dex*-amphetamine and closely related compounds (addiction potential & cardiovascular risk), serotonin releasers such as *dex*-fenfluramine/Redux® (pulmonary hypertension), and a combination of fenfluramine and the sympathomimetic drug phentermine, Pondimin® (cardiac valvulopathy). A similar fate has more recently befallen the cannabinoid CB1 receptor antagonist/inverse agonist rimonabant/Acomplia® (psychiatric risk) and the dual noradarenaline/serotonin reuptake inhibitor sibutramine/Merida®/Reductil® (cardiovascular risk).

Until very recently, therefore, European clinicians have been left with but a single approved anti-obesity medication; the pancreatic lipase inhibitor, orlistat (Xenical®). Weight loss with this compound tends to be modest (circa 3 kg in 12 months) but of sufficient magnitude to have beneficial effects on cardiovascular risk (e.g. Torgerson et al., 2004). Although relatively mild by comparison with other agents, adverse effects of reduced fat absorption include diarrhoea, flatulence, bloating, abdominal pain and dyspepsia (Bray and Greenway, 2007). Despite this bleak state of affairs, major advances in our understanding of the multiplicity of central and peripheral signalling mechanisms regulating appetite and