Targeting skeletal muscle to treat type 2 diabetes

As a result of the obesity epidemic, type 2 diabetes has emerged as a leading cause of mortality that continues to endanger global health due to its ever-increasing prevalence[1]. In fact, it has been estimated that over 700 million adults worldwide will have been diagnosed with this metabolic disease by 2045, thereby affecting nearly one in 10 people[2]. This will place a heavy economic burden on health-care funds worldwide, as type 2 diabetes significantly increases the likelihood of developing severe comorbidities, including cardiovascular diseases and cancer[3, 4]. The availability of highly effective treatments that can both prevent and even reverse type 2 diabetes is therefore of great importance. At present, lifestyle interventions that reduce the immense energy surplus in the body are considered to be the best strategies to improve disease progression[5]. Nevertheless, their application in a mostly obese population has proven difficult, and rates of non-adherence over prolonged periods of time are high[6], indicating that novel pharmaceutical therapies are urgently needed. In this article we describe a new approach for treating type 2 diabetes which has been developed by our Sweden-based company Atrogi AB. This involves targeting skeletal muscle with a long-acting glucose-lowering agent which recently started Phase 1a/b clinical trials.

The pathophysiological basis of type 2 diabetes lies in relative impairments in the body's ability to both secrete and respond to insulin, thereby negatively affecting whole-body glycaemic control[7]. These disturbances in glycaemic control are adversely associated with frequent and prolonged periods of hyperglycaemia which – in the long-term – drastically affect both micro – and macrovascular health, ultimately resulting in severe comorbidities commonly associated with type 2 diabetes[8]. Current pharmaceutical compounds are primarily aimed at diminishing continuous hyperglycaemia via distinct mechanisms of action, such as reducing hepatic glucose output or increasing renal excretion of glucose[9, 10]. Interestingly however, none of these conventional drugs counteract hyperglycaemia by directly affecting skeletal muscle glucose uptake and/or insulin sensitivity. This is especially intriguing as the skeletal muscle accounts for the majority of insulin-stimulated glucose disposal in day-to-day life[11] and a blunted skeletal muscle glucose uptake caused by insulin resistance is a key feature in the development of type 2 diabetes[12]. This suggests a potential to target skeletal muscle in order to improve glycaemic control in patients with this disease, which has thus far been underappreciated by the pharmaceutical industry.

The search for viable therapeutic targets to augment skeletal muscle glucose uptake and/or insulin sensitivity has been an active area of research. In this regard, recent studies have focused on the potential of the sympathetic nervous system to improve skeletal muscle insulin resistance and the accompanying blunted glucose uptake. Unlike its counterpart, which is active during periods of rest and digestion (i.e. the parasympathetic nervous system), the sympathetic nervous system promotes energy expenditure and the oxidation of substrates in various organs, including skeletal muscle[13]. Stimulation of the sympathetic nervous system could therefore markedly affect both skeletal muscle glucose uptake as well as insulin resistance, which is supported by several lines of evidence. Previous studies have demonstrated that activation of the sympathetic nervous system enhances skeletal muscle glucose uptake in rodents, independent of alterations in insulin concentrations[14-16]. Follow-up studies showed that the beta-2 adrenergic receptor (beta-2-AR) – an abundantly expressed beta-adrenergic receptor in skeletal muscle[17] – was the main mediator of these effects. Indeed, activation of these receptors via treatment with specific beta-2 agonists was shown to not only improve skeletal muscle glucose uptake *in vitro* and *in vivo*[18-20], but also to markedly improve glucose and insulin tolerance in rodent models of diabetes[20-26].

These research findings have sparked great scientific interest in the potential use of systemic beta-2 agonists to improve glycaemic control in type 2 diabetes patients. This enthusiasm increased following the publication in January 2023 of a study in *Nature Communications* by van Beek et al.[27], which demonstrated that treatment with the selective beta-2 agonist clenbuterol for 14 days significantly improved peripheral insulin sensitivity (primarily skeletal muscle) in healthy, young male volunteers. Based on these findings, the authors postulated that "prolonged treatment with a beta-2 agonist also has the potential to have marked beneficial effects on insulin sensitivity in volunteers with disturbed glucose homeostasis, such as in type 2 diabetes patients[27]".

Despite these promising findings, currently available systemic beta-2 agonists are not suitable for use in a clinical setting for several reasons. First of all, conventional systemic beta-2 agonists are generally characterised by their short half-life and low-specificity, which prevents prolonged and efficient stimulation of beta-2-ARs and thus hinders the effects on skeletal muscle glucose uptake. Secondly, currently available beta-2 agonists are known to have desensitising properties[28] indicating that their effects on skeletal muscle glucose uptake may diminish upon prolonged use. Finally, the use of these beta-2 agonists is often accompanied by various side effects[27, 29]. Commonly reported side effects include tremors in the hands, muscle stiffness, headaches or feelings of anxiety. Although non life threatening, these side effects could have a significant impact on a patient's overall quality of life. Most importantly, however, the use of conventional beta-2 agonists has been associated with adverse cardiovascular effects, including heart hypertrophy and increased blood pressure and in some cases, an increased risk for atrial fibrillation or cardiac arrest[30]. These effects drastically limit the use of these beta-2 agonists in a population already at risk for developing cardiovascular diseases. Although the use of systemic beta-2 agonists to improve glycaemic control in type 2 diabetes patients thus remains promising, we strongly believe that the pharmaceutical industry should focus on the development of highly selective, long-acting, systemic beta-2 agonists without desensitising properties and that limit the occurrence of side effects.

The ambition of Atrogi AB

Our company, Atrogi AB, was founded in 2013 for the purpose of developing a long-acting beta-2-AR agonist for the treatment of type 2 diabetes. This has led to the creation of the company's small molecule drug ATR-258. In preclinical studies, the drug has been shown to stimulate glucose uptake in skeletal muscle cells, independent of the signalling events causing the side effects commonly associated with currently available beta-2 agonists. With its unique mechanism of action, the pre-clinical data has demonstrated high levels of efficacy in treating type 2 diabetes and its associated comorbidities upon both acute and prolonged use, whilst simultaneously limiting the side effects. Based on these pre-clinical findings, ATR-258 has recently been approved by the German health authority (BfArM) for phase 1a/b clinical trials investigating the effects in type 2 diabetes patients. With the first patients already enrolled, the trial is expected to be completed before the summer with the final report available a couple of months later. If successful, ATR-258 could mark the beginning of a new class of anti-diabetic drugs, thereby taking a major step forward in the battle against diabetes.

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