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REVIEW ARTICLE

ALSUntangled #72: Insulin

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Abstract

ALSUntangled reviews alternative and off-label treatments for people living with amyotrophic lateral sclerosis (PALS). Here we review insulin, which has at least one plausible mechanism for slowing ALS progression. However, pre-clinical studies are limited and there have been no trials in PALS yet. Insulin use in patients without a metabolic need may cause very serious and potentially lethal side effects. While further studies to evaluate potential benefits may be warranted, at this time we cannot endorse insulin treatment to slow ALS progression.

Keywords: *Amyotrophic lateral sclerosis (ALS), insulin, metabolism, off-label treatment*

ALSUntangled reviews alternative and off-label ALS treatments on behalf of people living with amyotrophic lateral sclerosis (PALS). Here we review insulin, for which we had 415 requests (1).

Overview

Hormones are chemical signals produced by specialized organs and tissues of the body in response to environmental or developmental changes (2). Upon release into the blood, hormones are transported to their target organs where they bind to receptors on the surface or interior of target cells. Insulin is a large, negatively-charged, polypeptide hormone that is produced by specialized beta-cells of the endocrine pancreas in response to fluctuations of glucose concentration in the blood (3). The beta-cells package and store insulin in granules and release the

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stored insulin into the bloodstream in response to certain stimuli, such as increased glucose levels in the blood (3). In addition, the nervous system inhibits insulin secretion from beta-cells through sympathetic stimulation and enhances secretion through parasympathetic stimulation (3).

As a large, charged molecule, insulin cannot enter the target cell directly but needs to bind to a special receptor on the cell surface to influence the target cell. The insulin receptor is a member of the receptor tyrosine protein kinase (RTK) family. When insulin binds to the insulin receptor a cascade of events unfolds in the interior of the cell, leading to pleotropic effects downstream in cellular signaling pathways (2).

In skeletal muscle and adipose cells, insulin binding promotes glucose uptake from the blood by translocating the GLUT4 glucose receptor to the surface of the cells (4). In adipose tissue, this insulin-induced glucose uptake contributes to fatty acid and triglyceride synthesis (4). Insulin also causes the liver to store lipids by stimulating triglyceride synthesis and inhibiting triglyceride breakdown (4).

Understanding insulin's function in the central nervous system is an area of significant interest. Unlike in muscle and adipose tissue, glucose uptake in brain is largely due to insulin independent mechanisms. Nevertheless, the insulin receptor is expressed throughout the brain and may influence synaptic transmission, axon growth and neuroplasticity, protein synthesis, gene transcription, and neuronal polarity (4). In the past, ALS was often thought of as a disease that only affected motor neurons in the brain and spinal cord. As further understanding of the disease has evolved, metabolic abnormalities including alterations in glucose homeostasis and impaired insulin signaling, have been recognized in PALS (5–9).

Mechanisms

Glucose Metabolism

While abnormalities of glucose metabolism and impaired insulin signaling have been reported in PALS (5–11), it is uncertain whether these are contributing to the pathophysiology of the disease or are a result of the disease. Onset of Type 2 diabetes later in life (after age 50) has been associated with a lower risk of developing ALS and a delayed ALS onset (reviewed in 9). On the other hand, onset of Type 1 and possibly Type 2 diabetes earlier in life has been associated with a higher risk of ALS (reviewed in 9). No consistent effect of diabetes on progression or prognosis has yet been demonstrated (9). Compared to healthy controls, familial and sporadic PALS have been shown to have abnormalities in regional brain glucose metabolism on FDG PET (12); however, some areas appear hypermetabolic whereas others appear hypometabolic and these differ depending on the presence of C9ORF72 mutations and/or dementia (12). In a recent population-based case-control study, 2 antidiabetic drugs were associated with a significantly lower risk of developing ALS: metformin and glucagon (13). Insulin was apparently not examined in this study.

Connexin-43 (CX-43)

Astrocytes are specialized central nervous system cells that protect neurons (14). Astrocytic processes line the walls of the capillaries and form the blood brain barrier. Connexin 43 (Cx43) is an astrocyte protein that forms gap junction pores which, when open, may allow the transfer of toxic substances from astrocytes to motor neurons (15). Cx43 levels are elevated in the G93A mSOD1 mouse model of ALS (16), and survival in this model can be increased by astrocyte-specific Cx43 knockout (16). Furthermore, tonabersat, a Cx43 blocking drug, preserves motor neurons in the G93A mutant SOD1 mouse model of ALS (16). In silico modeling has recently shown that insulin could also bind to and block this channel (17).

Since insulin may be able to block the Cx43 pore, a target that is theoretically involved in ALS progression, we assign a Table of Evidence (TOE) "mechanisms" grade of C (Table 1).

Pre-Clinical Studies/Animal Models

In a Drosophila fruit fly model of C9ORF72 ALS, one group demonstrated that insulin receptor ligands were downregulated (18). Treatment with insulin prolonged the flies' survival (18). This was a well-designed study, but we have not found evidence of anyone attempting to replicate it. It is unclear how well findings in this model will translate into PALS, especially since most do not have repeat expansions. We found no pre-clinical studies of insulin treatment in any other model of ALS.

Based upon this single study in a C9ORF72 fly model of ALS, we assign a TOE "pre-clinical" grade of B.

Table 1. Table of evidence for insulin as an ALS treatment.

Category	Grade	Explanation
Mechanism	C	Insulin can possibly act on at least one biological mechanism (Cx43) that is theoretically relevant in ALS progression
Pre-Clinical	B	Insulin treatment prolonged survival in a single well-designed study using a C9ORF72 mutant fly model of ALS. This has not been independently replicated.
Cases	U	No known case reports to date.
Trials	U	No known trials to date
Risks	F	Insulin treatment can have frequent and severe side effects

Data in PALS

We found no case reports or clinical trials using insulin as a treatment for PALS. Thus, we assign TOE "cases" and "trials" grades of U (Table 1).

Of interest, we found a small trial of another anti-diabetic called pioglitazone in PALS (19). This trial showed no benefits on any measure of ALS progression (19). Since insulin may have mechanisms for slowing ALS that are independent of its effects on glucose, this trial does not rule out a possible benefit from insulin. There is also an ongoing trial (https://www.clinicaltrials.gov/study/NCT04220021?cond=ALS&term=metformin&rank=1_) of another anti-diabetic drug called metformin for patients with C9ORF72 ALS. The rationale for using this drug is based on its specific effects on toxic proteins caused by this genetic defect. Thus, this trial's results will not shed light on insulin's promise as an ALS therapy.

Also of interest, there have been several small trials of thyrotropin-releasing hormone (TRH) in PALS (reviewed in reference 19). TRH ultimately stimulates the release of other hormones including one called T3 which increases insulin synthesis and improves insulin sensitivity (20, 21). The fact that TRH administration produced no consistent, long-lasting benefits for PALS argues somewhat against the ability of insulin to slow ALS progression.

Finally, there have been studies on insulin-like growth factor 1 (IGF-1) in PALS. IGF-1 is similar in molecular structure to insulin, and though it binds to different receptors, it has overlapping effects on glucose lowering and improves insulin sensitivity and carbohydrate homeostasis (22). Some studies have shown inverse correlations between serum IGF-1 levels and ALS progression (23). But three trials of IGF-1 have been performed in PALS, with a meta-analysis finding no dramatic or consistent benefits on progression (24). There were methodological flaws in these trials that may limit conclusions (24), but these are certainly not supportive of the ability of insulin to slow ALS progression.

Dosing, Risks and Costs

Insulin is available in many formulations for treatment of diabetes including short-acting subcutaneous formulations, long-acting subcutaneous formulations, and a rapidly acting inhaled formulation (see Table 2, reference 25.26). Dosing varies based on the needs of each patient.

The risks of insulin therapy in patients with diabetes are primarily hypoglycemia, but hypokalemia, weight gain, anaphylaxis, myalgia, itch, and rash may also result (25). Symptoms of hypoglycemia may include sweating, weakness, tachycardia, paresthesia, irritability, confusion, transient focal neurological defects, seizure, loss of consciousness (27) and death. There are additional risks of inhaled insulin due to the route of delivery. These include a possible decline in pulmonary function (i.e., FEV1), cough (reported in up to 44% of patients), and possible increase in lung cancer risk and mortality (26). Inhaled insulin risk is thought to be higher in patients with asthma or chronic obstructive lung disease (26). Due to the possibility of inhaled insulin worsening lung function, it could accelerate respiratory failure in PALS.

Table 2. Common formulations of insulin.

Insulin type	Onset of action	Duration
Fast Acting Lispro, aspart, glulisine, regular	15-30 minutes	4-6 hours
Long Acting NPH, Glargine, detemir	Varies based on preparation, in general 1-2 hours	6-24 hours
Inhaled Rapid Acting Afrezza	15 minutes	1-4 hours

Based upon the high frequency of potentially serious side effects of insulin therapy, we assign a TOE "risks" grade of F (Table 1).

Over 9 million people in America take insulin. The average cash price per unit of insulin in 2023 is approximately $0.30, up from $0.22 in 2014 (28). However, the approval of generic and biosimilar insulin may lead to an overall decrease in price (28). The prices of insulin also vary by formulation often with the newer formulations costing more. For example, inhaled insulin can be up to 20 times more costly per unit compared to fast acting subcutaneous alternatives (26). Therefore, costs are variable and can be quite significant.

Conclusions

Insulin treatment for ALS is an intriguing area for future research. However, the risks of insulin administration are significant and potentially lethal. Currently, there is no clinical evidence to support its use in PALS. Therefore, we cannot endorse insulin as way to slow, stop or reverse ALS progression at this time.

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