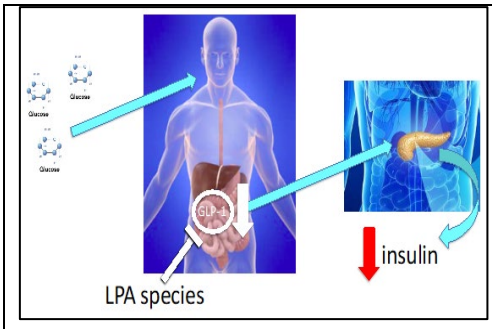
UNIVERSITY OF WATERLOO

TECHNOLOGY SUMMARY



Reference
(Project. 10173)

Inventor(s)
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Stage of development
Prototype with ongoing research

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Restoring GLP-1 incretin to treat Type 2 Diabetes mellitus and obesity

Background
Glucagon-like peptide 1 (GLP-1) is a hormone secreted by L-cells of the gastrointestinal tract in response to incoming glucose. GLP-1 is referred to as an incretin, which serves to potentiate insulin secretion by beta-cells of the pancreas, ensuring that adequate amounts of insulin are released to allow for proper disposal of glucose after consuming a meal. Healthy beta-cells fail to secrete enough insulin when incretin levels do not rise. It is known that GLP-1 levels and action are reduced/impaired in obesity and in Type 2 Diabetes Mellitus (T2DM). People with obesity and T2DM often exist in a state of elevated chronic subacute inflammation.

Description of the invention
To date, only two negative regulators of GLP-1 secretion have been identified (i.e. the hormone somatostatin and the neuropeptide galanin). This invention demonstrates that a compound that is produced in inflammation, called lysophosphatidic acid (LPA), can also drastically inhibit GLP-1 secretion by L-cells. LPA is produced directly in atherosclerotic plaques, and it contributes to worsening of cardiovascular disease. It also goes up steadily as people become more and more overweight. Inflammation, obesity, and cardiovascular disease are frequently comorbid with Type 2 diabetes mellitus (T2DM). T2DM is considered an inflammatory disease, and there is evidence that inflammation precedes development of T2DM and makes it worse. Waterloo researchers have found that when LPA signaling is blocked using LPA inhibitors, such as LPA-receptor antagonists, the reduction in GLP-1 secretion can be prevented. Therefore LPA-receptor antagonists are expected to beneficially raise GLP-1 as a means of treating T2DM and possibly other diseases associated with low GLP-1 (eg. atherosclerosis, diabetic retinopathy, nephropathy, and obesity).

Advantages
Two classes of pharmaceuticals are currently used to improve the efficacy of GLP-1: GLP-1R agonists and dipeptidylpeptidase 4 (DPP4) inhibitors. GLP-1R agonists have side-effects that include nausea, vomiting, diarrhea, headache, weakness and dizziness and nasopharyngitis. Exenatide, a GLP-1R agonist, may worsen kidney disease. Adverse effects of DPP-4 inhibitors include GI problems (nausea, diarrhoea, and stomach pain), flu-like symptoms (headache, runny nose, sore throat) and skin reactions. Thus, the use of LPAR antagonists restores the body's natural mechanism to produce GLP-1 without the side effects associated with GLP-1R agonists and DPP4 inhibitors.

Potential applications
Therapeutic for the following diseases & symptoms which are expanding due obesity and aging:

- Type 2 diabetes mellitus (T2DM)
- Cardiovascular (Atherosclerosis)
- Treatment of obesity
- Alzheimer's disease, and associated comorbidities
- Kidney disease
- Obesity