Effect of salsalate on lipid induced insulin resistance

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Using the model of lipid-induced insulin resistance we will study the hypothesis that pre-treatment with salsalate (salicylsalicylic acid) blunts the development of lipid-induced insulin resistant in an I*B/NF*B dependent manner in healthy human...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON30763

Source
ToetsingOnline

Brief title
lipid induced insulin resistance

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
insulin resistance, resistance against the action of insulin

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: NWO

Intervention

Keyword: insulin resistance, lipid infusion, salsalate

Outcome measures

Primary outcome

As an outcome measurement, insulin sensitivity will be assessed by means of a hyperinsulinemic euglycemic clamp.

Secondary outcome

The following outcome parameters will be assessed: inflammatory markers, salsalate downstream genes, proteins involved in lipid handling (PKC), lipid metabolites in skeletal muscle; insulin sensitivity (hyperinsulinemic-euglycemic clamp); oxidative capacity (aerobic exercise test); body composition; mitochondrial markers and peripheral lipid accumulation in muscle (muscle biopsies); expression of proteins involved in fatty acid handling and insulin signalling in skeletal muscle (muscle biopsies).

Study description

Background summary

Insulin resistance is a primary factor causally linked to the pathogenesis of type 2 diabetes. Skeletal muscle accounts for a substantial part of the total body mass, and is responsible for ~80% of insulin-stimulated glucose uptake. There is evidence that accumulation of fat in non-adipose tissues, like heart, liver and muscle contributes to development of insulin resistance in non-trained individuals. Thus, intramyocellular lipids (IMCL) are tightly correlated with the severity of insulin resistance and it has been shown that intracellular fatty acid metabolites, like diacylglycerol (DAG), long-chain fatty acyl CoA (LCFACoA) and ceramides, may cause insulin resistance by activation of the serine/threonine kinase PKC, which impedes insulin signaling

at the level of insulin receptor substrate-1 (IRS1). Next to PKC-induced inhibition of insulin signaling, intracellular fatty acid metabolites can activate the inflammatory I*B/NF*B pathway, which is also associated with the development of insulin resistance. Under resting conditions cytosolic NF*B is bound to its inhibitor protein subunit, I*B. Upon activation of I*B kinase (IKK) I*B gets phosphorylated and degrades, disinhibiting NF*B. Than NF*B translocates to the nucleus where it binds to its target genes and increases the expression of chemokines, proinflammatory cytokines and inflammatory enzymes. which in a feedforward loop also activates NF*B, leading to a progressive inflammatory responses, and a deterioration of insulin resistance. Interestingly, chronic low-grade inflammation is also associated with insulin resistance and the use of high-doses non-steroidal anti inflammatory agents like Aspirin (acetylsalicylic acid) or salsalate (a non-acetylated dimer of salicylic acid which, in contrast to Aspirin, does not affect COX activity and therefore bleeding time) can improve glycemic control as indicated by decreased fasting glucose levels, a decrease of glycosuria and an increase in insulin secretion. The mechanism underlying the insulin sensitizing effect of acetylsalicylic acid is not yet known, although recent animal research implicates a role for IKK: after inhibition of IKK, the I*B/NF*B pathway remained inactivated and insulin resistance improved. In contrast, overexpression of IKK led to activation of this pathway and resulted in an increase in insulin resistance.

Study objective

Using the model of lipid-induced insulin resistance we will study the hypothesis that pre-treatment with salsalate (salicylsalicylic acid) blunts the development of lipid-induced insulin resistant in an I*B/NF*B dependent manner in healthy human subjects. Using this approach we will be the first to examine the effects of an anti-inflammatory agent (salsalate) on acute low-grade inflammation in muscle upon acute lipid-induced insulin resistance and to identify targets for early intervention towards the development of type 2 diabetes.

As such, we would like to get more insight in the pathogenesis of insulin resistance which would lead to a better understanding of type 2 diabetes mellitus and to the prevention and treatment of this disease.

Study design

Subjects will be invited for a screening visit which will include measurement of body composition and a maximal aerobic exercise test. Subsequently, all subjects will undergo two hyperinsulinemic euglycemic clamps with simultaneous infusion of LCT separated by at least 1 week and in a random order. In one of these trials, subjects receive in the 4 preceding days of the clamp 4 g salsalate a day. In the other trial, salsalate will be replaced by placebo

tablets. In addition to these two hyperinsulinemic euglycemic clamps with simultaneous infusion of LCT, a third hyperinsulinemic euglycemic clamp will be performed without simultaneous infusion of LCT and will serve as a control trial.

Intervention

Disalcid is insoluble in acid gastric fluids but readily soluble in the small intestine where it is partially hydrolyzed to two molecules of salicylic acid. In contrast to acetylsalicylic acid (better known as aspirin), the use of Disalcid is much safer: acetylsalicylic acid inhibits the cyclooxygenase (COX) activity, resulting in decreased synthesis of prostaglandin, leukotriene and thromboxane precursors such as the ubiquitous enzyme which catalyzes the initial step in the synthesis of prostanoids. Low stomach prostanoid levels strongly increases the risk of ulceration, internal bleeding and perforation of the stomach. Therefore, salsalate will be used in this study.

In this study, the effect of salsalate on insulin resistance will be investigated. All subjects will undergo three hyperinsulinemic euglycemic clamps. Two hyperinsulinemic euglycemic clamps will be with simultaneous infusion of lipids, separated by at least 1 week and in a random order. In one of these trials, subjects receive in the 4 preceding days of the clamp 4 g salsalate a day. In the other trial, salsalate will be replaced by placebo tablets. In addition to these two hyperinsulinemic euglycemic clamps with simultaneous infusion of lipids, a third hyperinsulinemic euglycemic clamp will be performed after the intake of placebo tablets, but without simultaneous infusion of lipids. This trial will serve as a control trial.

Study burden and risks

Blood samples, infusions and muscle biopsies might cause bruises. Infections or continued bleeding are exceptional. The subjects will be instructed to refrain from heavy physical labour and not to remove the pressure bandage for at least 24 hours after the biopsy. Biopsies will be taken by a skilled medical doctor.

Hyperinsulinemic euglycemic clamping is a procedure we perform routinely in our laboratory without notable complications. In rare occasions subjects exhibit symptoms of hypoglycaemia (even if their blood glucose levels are still above 3 mmol). In these occasions insulin infusion will be terminated until normoglycemia is achieved. After successfully performing the clamp blood glucose values will be monitored for an additional 30 minutes with glucose infusion stand-by if glucose levels happen to drop. Solid food will be provided directly after finalising the clamp to avoid the experience of hypoglycaemia.

Infusion of Intralipid is routinely used in clinical settings. Adverse effects are rare but nausea, vomiting, diarrhoea, shivering and fever might occur

during long term administration of intralipid. Given the sort time span of infusion in the present study (less than 6 hours) we anticipate no such adverse effects. If they happen to occur anyway, the infusion will be terminated promptly.

Salsalate is a drug which in general is well tolerated without major risks. The following reversible adverse experiences characteristic of salicylates were most commonly reported with Disalcid, listed in descending order of frequency: tinnitus, nausea, hearing impairment, rash, and vertigo. Although cause-and-effect relationships have not been established, spontaneous reports over a ten-year period have included the following additional medically significant adverse experiences: abdominal pain, abnormal hepatic function, anaphylactic shock, angioedema, bronchospasm, decreased creatinine dearance, diarrhea, gastro intestinal bleeding, hepatitis, hypotension, nephritis and urticaria. The usual dosage is 3000 mg daily, divided over three dosages. However, studies by the group of Shoelson revealed that a dose of 4000 mg was required for insulin sensitizing effects. Therefore, the dosage of salsalate intake in this investigation will be 4000 milligrams daily. Previous investigations showed no additional side effects after the intake of 4000 mg of salsalate/day.

As drug interaction of Disalcid is recognized, use of any medication is an exclusion criterion. Given the fact that Disalcid has additive effects to aspirin and other salicylate derivates, special care will be taken to exclude the use of any NSAID during the study. Furthermore, the intake of salsalate should be avoided in following conditions: before (dental) surgery, anaemia, bleeding problems, ulcers, asthma, kidney or liver disease, gout, Hodgkin*s disease, nasal polyps flu symptoms, chickenpox or when a subject is allergic to salsalate, aspirin or other medications for arthritis, pain, or any other drugs. Finally, it is not allowed to take aspirin, or drink alcohol while taking salsalate.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Male sex
- Age 18-30 years
- BMI 20-25 kg/m2
- Stable dietary habits and physical activity levels

Exclusion criteria

- Family history of diabetes
- Medication use
- Allergic to salsalate
- Allergic to aspirin
- Alcohol intake during 4 days prior to the clamp
- Stomach ulcer
- Impaired kidney function

Study design

Design

Study type: Interventional

Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-11-2007
Enrollment:	10
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Disalcid
Generic name:	Salsalate

Ethics review

Approved WMO

Date:	16-05-2007
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2006-007012-22-NL
CCMO	NL13861.068.07