profil
ANSWERS FOR DIABETES

Methodology fact sheet: 2-step insulin sensitivity clamp

Background

- → The loss of insulin sensitivity and insulin secretion are key drivers of type 2 diabetes progression.
- → 2-step hyperinsulinemic euglycemic clamps (2-step insulin sensitivity clamps) are considered gold standard for the assessment of peripheral insulin resistance in clinical diabetes research.
- → To prove whether lifestlyle and pharmacological interventions restore peripheral insulin sensitivity, 2-step hyperinsulinemic clamps can be used.

Why measure peripheral insulin resistance?

Peripheral insulin resistance, i.e. insulin resistance of muscle and fat tissue, plays a role in the progression of type 2 diabetes. Innovative pharmacologial interventions pursue the goal of restoring insulin sensitivity. The impact on insulin resistance of muscle and fat tissue should be proven early in clinical development. Depending on the outcome further investigations may yield valuable insights into insulin sensitivity at the level of the liver and adipose tissue.

Why are 2-step insulin sensitivity clamps the method of choice for the assessment of peripheral insulin resistance?

2-step insulin sensitivity clamps enable the measurement of peripheral insulin sensitivity adjusted for glucose effectiveness (i.e. the mass effect of glucose on glucose utilization). Unlike oral and intravenous glucose tolerance tests 2-step insulin sensitivity clamps allow for assessment of insulin sensitivity at steady-state serum insulin concentrations.

How does a 2-step insulin sensitivity clamp experiment work?

Profil uses the algorithm-powered closed-loop control system ClampArt® in order to achieve a fully automated adjustment and maintenance of a pre-defined blood glucose concentration, i.e. the glucose clamp level. Under this condition a 2-step infusion insulin is established for the consecutive adjustment of two steady state serum insulin concentrations ($[INS_2] > [INS_1]$) with corresponding glucose infusion rates ($GIR_2 > GIR_1$).

What data can you get out of the 2-step insulin sensitivity clamp?

At each steady state M values (GIR divided by body weight), metabolic clearance rates (MCR, M values divided by the clamped blood glucose concentration $[BG_{Clamp}]$), as well as insulin sensitivity indices ($ISI_{Glucose}$: M value divided by steady state serum insulin concentration) can be calculated. The peripheral insulin sensitivity adjusted for glucose effectiveness (SI) is calculated as follows:

$$SI = (M_2\text{-}M_1)\cdot([INS_2] - [INS_1])^{-1}\cdot[BG_{Clamp}]^{-1}$$

Did you know?

The 2-step insulin sensitivity clamp adjusts peripheral insulin sensitivity for glucose mass effects on glucose utilization (glucose effectiveness).

Important!

As compared to oral and intravenous glucose tolerance tests 2-step insulin sensitivity clamp assessments rely on metabolic assessments at steady state.

Other considerations

The usage of ClampArt® integrates the high standards of an algorithm-powered automated glucose clamp into the assessment of insulin sensitivity.

Related methods and their combination opportunities

Combined with isotope labeled glucose or glycerol infusion, hepatic and adipose tissue insulin resistance can be measured.

Advantages of the 2-step insulin sensitivity clamp

- → Accurate assessment of insulin sensitivity under steady state conditions
- → Elimination of the hepatic component of insulin resistance by the first-step insulin infusion
- → Glucose effectiveness can be calculated by the differential between the two steady states under the condition of glucose clamping
- → Possibility to calculate the Disposition Index which relates insulin resistance to insulin secretion disorder.

Disadvantages of the 2-step insulin sensitivity clamp

- → High levels of expertise and experience required

Conclusion

The 2-step hyperinsulinemic euglycemic glucose clamp is the gold standard method for the assessment of peripheral insulin sensitivity in different populations – it can be combined with various other methods for further assessments, depending on trial product and research question.

Further reading

1. Aleglitazar, a dual peroxisome proliferator-activated receptor-α/γ agonist, improves insulin sensitivity, glucose control and lipid levels in people with type 2 diabetes: findings from a randomized, double-blind trial. Diabetes Obes. Metab. 18(7):711-715, 2016.
2. Heise, T., Zijlstra, E,. Nosek, L., Heckermann, S., Plum-Mörschel, L., Forst, T. Euglycaemic glucose clamp: What it can and cannot do, and how to do it. Diabetes Obes. Metab. 18(10):962-972, 2016.
3. Schliess, F. 2017. Glucose clamps: 2 steps towards insulin sensitivity adjusted for glucose effectiveness. Profil Blog. https://blog.profil.com/blog/glucose-clamps-2-steps-towards-insulin-sensitivity-adjusted-glucose-effectiveness

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