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Summary

User guide to mechanism of action of glp-1 gip glucagon triple agonists

Ruben Nogueiras

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The speaker presented laboratory and clinical evidence suggesting that GLP-1 and GIP-based therapies improve NASH resolution but show limited efficacy against liver fibrosis, proposing that their hepatic benefits are indirect and that adding glucagon may be necessary for direct liver effects.

KEY POINTS

- The speaker reported that semaglutide resolves NASH in some patients but shows minimal improvement in liver fibrosis stage, with effects similar to placebo in larger studies.
- Tirzepatide, a dual GLP-1/GIP agonist, achieved up to 62% NASH resolution at the highest dose in a recent study, but improvement in fibrosis stage remained modest (55% versus 30% placebo, as stated by the speaker).
- The speaker's laboratory experiments found that liraglutide, GIP, and dual agonists did not reduce lipid content in human hepatocytes or reduce fibrotic markers in hepatic stellate cells when tested directly in vitro.
- The speaker proposed that GLP-1 and GIP act indirectly on the liver by reducing adiposity, improving insulin sensitivity, and decreasing systemic inflammation, since GLP-1 and GIP receptors are not expressed in liver tissue.
- The speaker noted that glucagon receptor is expressed in the liver and that dual GLP-1/glucagon and triple agonists (GLP-1/GIP/glucagon) reduced liver fat in clinical studies, though those patients did not have NASH with fibrosis.
- The speaker indicated that second-generation triple agonists show greater efficacy than first-generation compounds in pre-clinical studies for body weight and food intake reduction.

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