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Stimulation of thyroid hormone synthesis by ethyl-2-(4-(4-(5-amino-6-(tert-butylcarbamoyl)-2-(methylthio)thieno[2,3-d]-pyrimidin-4-yl)phenyl)-1H-1,2,3-triazol-1-yl) acetate (TPY3m) and thyroliberin in aging normal and obese rats

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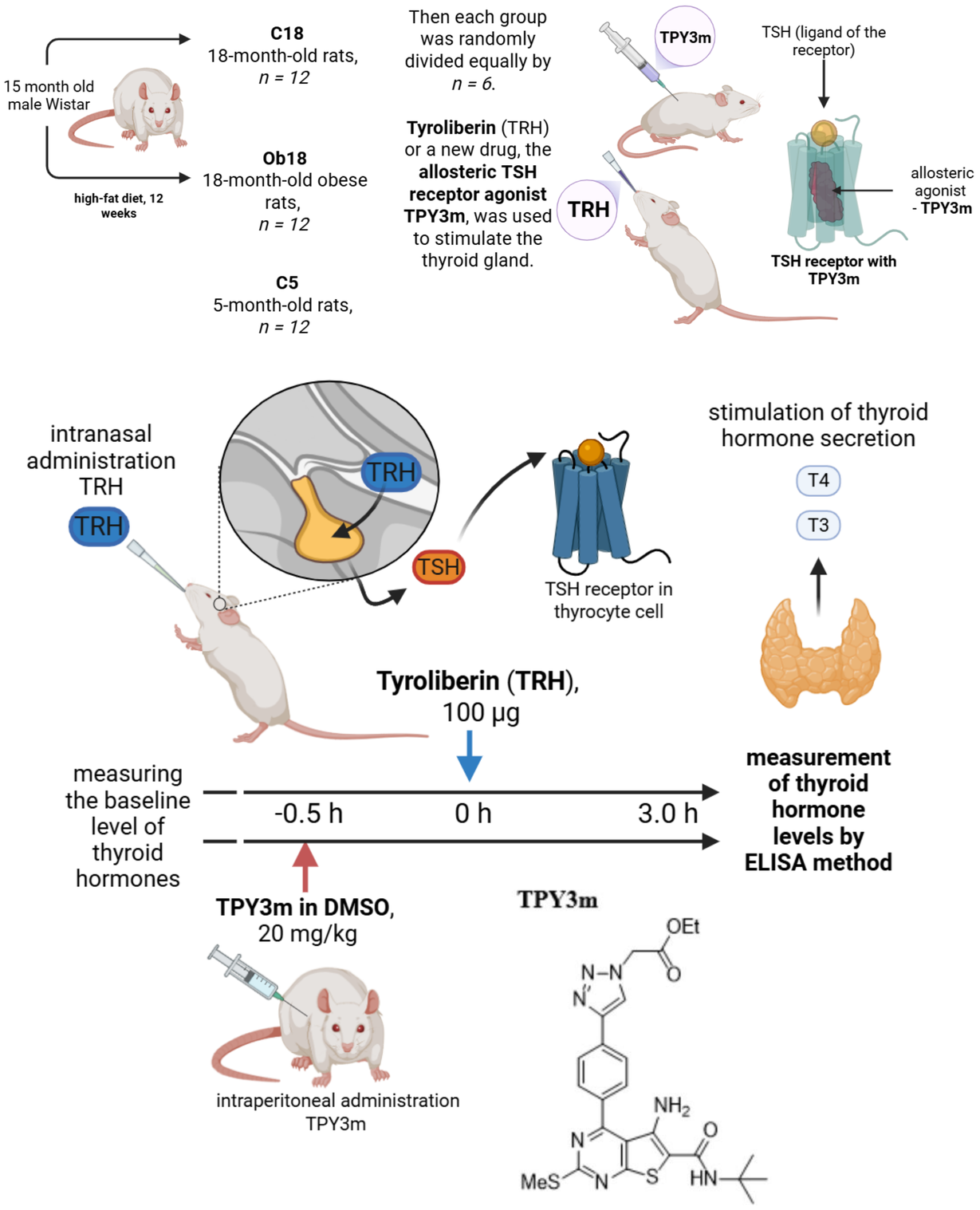
INTRODUCTION & AIM

Aging, and particularly obesity, lead to impaired thyroid function. This is manifested by thyroid resistance to thyrotropin (TSH) and a deficiency of thyroid hormones (T3, T4).

TPY3m is an allosteric agonist of the TSH receptor developed by our team. The aim of this study was to **investigate the effect of TPY3m on the thyroid status in aging** (18-month-old) **male Wistar rats, with and without obesity, during a thyrotropin-releasing hormone (TRH) stimulation test**.

METHOD

A total of 36 rats were used. **Obesity** was induced via a 12-week high-fat diet. Animals received TPY3m (20 mg/kg, i.p.) and TRH (100 mcg/rat, i.n.). Serum concentrations of fT4, fT3, tT3, and TSH were quantified by enzyme immunoassay.



RESULTS & DISCUSSION

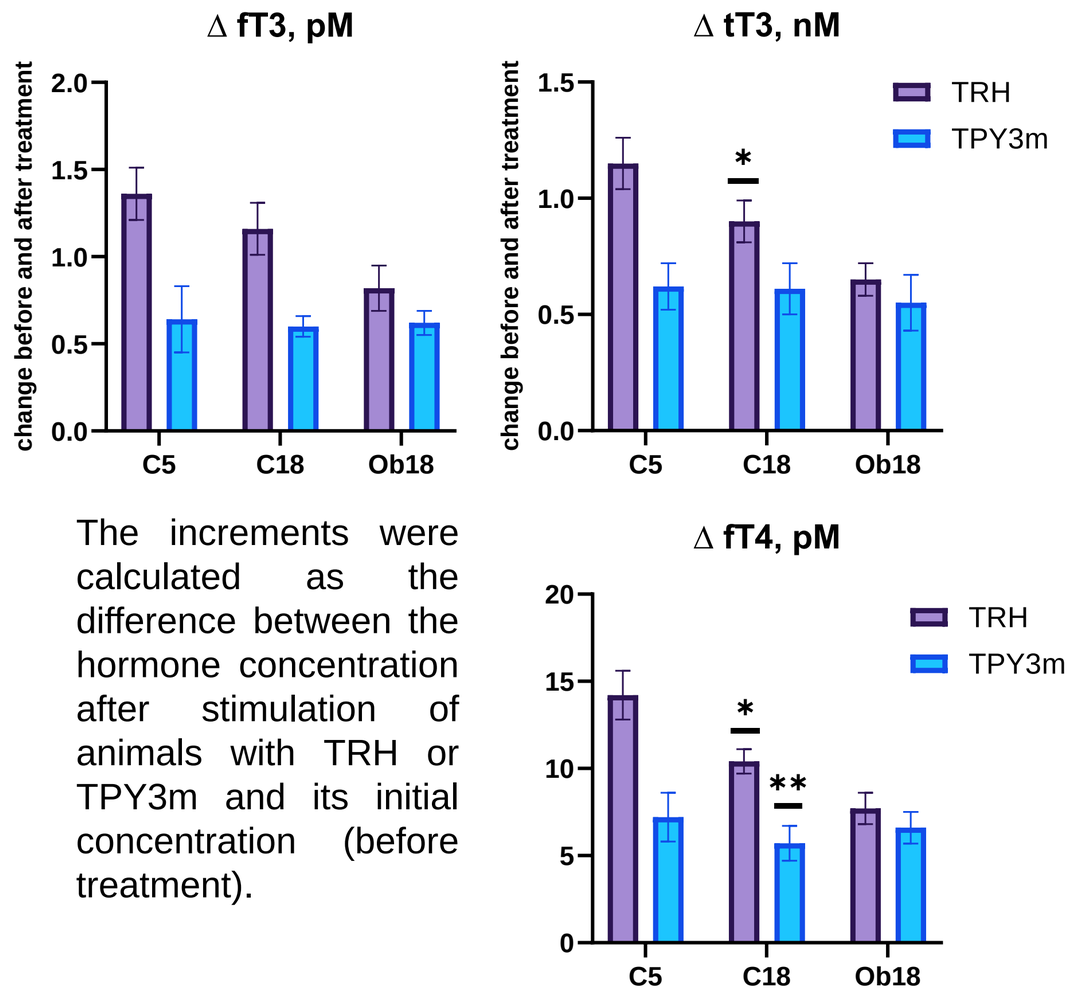
- **TSH Resistance in Aging & Obesity:** 18-month-old obese rats developed TSH resistance (↓fT4, ↓fT3, ↑TSH by 76%), with age alone having a minimal effect.
- **Aging & Obesity Blunt TRH Response:** The thyroid hormone response to TRH was impaired by both aging and obesity, despite a preserved TSH surge.
- **TPY3m: A Universal Agonist.** The efficacy of TPY3m was unaffected by obesity, age, or baseline thyroid status, demonstrating its robust therapeutic potential.

Levels of thyroid hormones and TSH in the blood of aging obese and non-obese rats compared with young animals without treatment

Hormone levels	C5 control group, age 5 months, *n = 12*	C18 control group, age 18 months, *n = 12*	Ob18 obesity, age 18 months, *n = 12*
fT4, pM	27.1±0.6	26.0±1.0	22.8±1.3#
fT3, pM	3.30±0.10	3.03±0.17*	2.42±0.13#
tT3, nM	2.37±0.13	2.13±0.10	1.97±0.11
TSH, µIU/mL	0.85±0.16	1.07±0.14	1.88±0.26#

Data are presented as mean ± SEM. * p < 0.05 C18 vs. C5 group;
# p < 0.05 C18 vs. Ob18 group;

Increases in fT4, fT3, and tT3 levels during treatment with TRH and TPY3m in young rats and aging animals with and without obesity.



The increments were calculated as the difference between the hormone concentration after stimulation of animals with TRH or TPY3m and its initial concentration (before treatment).

CONCLUSION

TPY3m is a promising compound for the development of drugs to correct thyroid hormone deficiency in cases where there is TSH resistance.