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TSH Receptor small molecule "drug-like" antagonists

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Graves' disease (GD) is caused by persistent, unregulated stimulation of thyroid cells by thyroid-stimulating antibodies (TSAbs) that activate the TSH receptor (TSHR). We identified the first small molecule "drug-like" TSHR antagonists, which inhibit TSH- and TSAb-stimulated signaling, and the first TSHR inverse agonists, which are antagonists that inhibit basal (agonist-independent) TSHR signaling in addition to TSH- and TSAb-stimulated signaling. To be used as therapy for GD, it would be important that an antagonist inhibits TSHR activation by the majority of TSAbs. The inverse agonist inhibited stimulated cAMP production by an average of 61% by all thirty GD sera tested. Furthermore, the inverse agonist inhibited basal and GD sera-induced up-regulation of the expression of thyroperoxidase mRNA in primary cultures of human thyrocytes by 65%. Another potential clinical application of a TSHR antagonist beyond treatment of the hyperthyroidism of GD could be alleviating the signs and symptoms of Graves' ophthalmopathy (GO), a disease of the eye found in GD patients in which there is overproduction of hyaluronic acid. We showed that the inverse agonist reduced TSH- and TSAb-stimulated cAMP production and hyaluronic acid production in Graves' orbital fibroblasts. Furthermore, we demonstrated *in vivo* in mice that an improved and selective inverse agonist decreased endogenous serum free T4 levels and lowered the increase in free T4 stimulated by a human TSAb. This inverse agonist lowered mRNAs for sodium-iodide transporter and thyroperoxidase in the thyroid also. Our results provide proof-of-principle for effectiveness of small molecule TSHR antagonists, including inverse agonists, *in vitro* and *in vivo* and may lead to an orally active drug that targets the TSHR directly to treat GD and GO.

Biography

Susanne Neumann, PhD has been working as a Staff Scientist at the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) at the National Institutes of Health in Bethesda, Maryland since 2006. She obtained her PhD in Biochemistry in 2000 at the University of Leipzig in Germany. Following her PhD training and a postdoctoral position in Leipzig she joined the NIDDK as a visiting postdoctoral fellow in 2002 and remained at NIDDK as a Staff Scientist in the Laboratory of Endocrinology and Receptor Biology. She is a member of the German Society of Endocrinology (DGE) and the American Thyroid Association. In 2001 she received the Merck European Thyroid van Basedow Research Prize.

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