PRX-3140, a 5-HT4 Agonist and Sigma-1 Agonist/Antag., Modulates Glucocorticoid Insulin Suppression and Cortisol Levels

Nanopharmaceutics Announces Preprint "PRX-3140, a 5-HT4 Agonist and Sigma-1 Agonist/Antag., Modulates Glucocorticoid Insulin Suppression and Cortisol Levels"

ALACHUA, FL, UNITED STATES, December 12, 2024 /EINPresswire.com/ -- Nanopharmaceutics, Inc., a clinical-stage pharmaceutical development company, announced submission of Preprint "PRX-3140, a 5-HT4 Partial Agonist and Sigma-1 Agonist/Antagonist, Modulates Glucocorticoid Insulin Suppression and Cortisol Levels" to medRxiv. The article has been submitted for peer review in a major journal.

ABSTRACT: PRX-3140 is a partial agonist to the 5-hydroxytryptamine receptor 4 (5-HT4) and a ligand for the sigma-1 (S1R) and sigma-2 (S2R) receptors. Although few publications have inferred S1R agonists/antagonists modulate blood glucose, Di et.al (2017) reported S1R deficiency in knockout mice impacted regulation of the hypothalamic-pituitary-adrenocortical (HPA) axis, with a dexamethasone-induced reduction in level of corticosterone markedly attenuated in S1R −/− knockout mice, implicating S1R in feedback response to the HPA axis. The hypothesis that S1R deficiency causes down-regulation of the glucocorticoid receptor (GR) and attenuates GR-mediated feedback inhibition of HPA axis, as well as stress response of HPA axis, suggest that the inverse, the activation of S1R under normal conditions, may modulate glucocorticoid insulin suppression (as a direct S1R-GR effect) as well as cortisol levels (producing HPA axis feedback inhibition). In the present study, coadministration of 10 μM PRX-3140 with 100 nM cortisol significantly increased insulin release (to 74.8 ng/ml, P-value <0.0001). Similar effects were observed when cells were exposed to dexamethasone (Dex), with 10 μM PRX-3140 and 10 nM Dex producing 1.87-fold significantly more insulin than 10 nM Dex alone. Daily glucose concentrations in the 14-day clinical study (NCT00384423) of PRX-3140 demonstrate a reduction for 10 mg once-daily at days 1, 7, 10, and 15. Urine free cortisol levels at 10, 30, 100 and 200 mg dose levels of PRX-3140 demonstrated a larger reduction at 7 and 14 days compared to placebo. As an agonist of S1R that acts as a chaperone of GR, PRX-3140 has demonstrated GR modulating effects in INS-1 cells and in 14-day clinical studies in healthy adults with low incidence of side effects. The results of the present study suggest that S1R activation, with PRX-3140 and NP-18-2 S1R agonists, modulates glucocorticoid insulin suppression and cortisol levels.

About Nanopharmaceutics, Inc.
Nanopharmaceutics, Inc. is a clinical-stage specialty pharmaceutical company developing oral,

topical, and injectable products for cancer, central nervous system (CNS) disorders, and infectious diseases. Nanopharmaceutics, Inc. is a wholly-owned subsidiary of TRON Pharmaceuticals, Inc. (OTC:TGRP)

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