Extended Abstract Journal of Medical Toxicology 2020
Vol.3 No.1

Toxicology-2020: Pituitary-Directed Drug Therapy for the Treatment of Cushing's disease: A Review Article- Michael Crider Department of Pharmaceutical Sciences, School of Pharmacy, Southern Illinois University Edwardsville, USA

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Cushing's disease (CD) is usually the result of an adrenocorticotropic hormone-secreting pituitary adenoma. The result is overstimulation of the adrenal glands leading to chronic hypercortisolism Individuals with CD have increased risks of hypertension, obesity, hyperglycemia, infections, and vascular damage. Transsphenoidal surgery of the pituitary adenoma is the preferred option in the treatment of CD. The success rates are 65- 90% for microadenomas; however, as many as 40% of patients will experience recurrence within 10 years.

Three types of agents are either under clinical investigation or approved that are pituitary-directed therapies. These include the peroxisome proliferator-activated gamma (PPARγ) agonists rosiglitazone and pioglitazone, the dopamine D2 agonist cabergoline, and the somatostatin peptidomimetic pasireotide. PPARγ agonists such as rosiglitazone and pioglitazone have demonstrated antiproliferative and apoptotic effects. Clinical studies with rosiglitazone and pioglitazone have involved a small number of patients and little change in cortisol levels has been observed.

Furthermore, the increased risks of cardiovascular side effects make PPARγ agonists less than ideal in the treatment of CD Since dopamine D2 receptors are found in approximately 80% of corticotroph adenomas, the D2 receptor agonist cabergoline has been evaluated in small clinical studies involving CD patients. In a study with 20 patients, cabergoline caused a sustained reduction in cortisol levels in 40% of patients after two years of treatment. Somatostatin (somatotropin release-inhibiting factor, SRIF) is a cyclic tetra decapeptide that occurs in two biologically active forms, SRIF-14 and a N-terminally extended form SRIF-28. SRIF exerts a variety of inhibitory actions including inhibition of insulin and glucagon release from the pancreas and growth hormone release from the pituitary. SRIF also exhibits antiproliferative actions, and it acts as a neurotransmitter or neuromodulator. SRIF exhibits its diverse pharmacological actions by binding to a family of structurally related G-protein-coupled receptors designated sst1-sst5. SRIF-14 and SRIF-28 bind with high affinities to all five SRIF receptor subtypes; however, the therapeutic effectiveness of the natural SRIF forms is limited by rapid proteolytic degradation.

Thus development of more metabolically stable analogues is of intense interest .Structure activity studies of SRIF-14 have shown that Trp8 and Lys9 comprise the critical β-turn and that Lys4, Phe6, Phe7, and Phe11 are important for binding to the five SRIF receptor subtypes. Utilizing the essential structural features of SRIF-14, a stable cyclohexapeptide with high affinity (0.1-10 nM) at sst1, sst2, sst3, and sst5 was discovered Formerly designated SOM230,thiscyclichexapeptide (cyclo[(4R)-4 2aminoethylcarbamoyl)-L-prolylLphenylglycyl-D-tryptophyl- L-lysyl-4-O-benzyl-L-tyrosyl-L-phenylalanyl-]). Although pasireotide binds to four of the five SRIF receptor subtypes, activation of sst5 is thought to be especially significant in inhibiting ACTH release in ACTH-secreting pituitary adenomas. In a phase III study involving 162 patients treated with either 600 μg or 900 μg two times a day, pasireotide was shown to significantly reduce cortisol levels in CD patients. Although transsphenoidal surgery is the preferred first choice of treatment, many CD patients are not controlled by this procedure. As a result, pituitary-directed therapies offer a significant alternative for those individuals. The recent approval of pasireotide offers another option for those individuals in which surgery is not possible or has failed. Although hyperglycemia is a major adverse effect with pasireotide, it seems possible to treat this with antidiabetic drugs. Additional studies are needed to determine the effectiveness of combination therapies such as cabergoline and pasireotide. In conclusion, new drug therapy as exemplified by pasireotide offers new hope for combating CD.

This work is partly presented at Joint Event on, Pharmacology & Medical Toxicology February 25-26, 2020