The Dual SSTR2/5 Specific Somatostatin Analog, AP102, Does Not Affect Glucose Metabolism in Diabetic ZDF Rats: A Comparative 14-Day Infusion Study Versus Pasireotide

Adrian F. Daly [1], Mark Sumeray[2]

[1]Department of Endocrinology, CHU de Liège, University of Liège, Liège, Belgium; [2]Amryt Pharma, Fitzwilliam Hall, Fitzwilliam Place, Dublin, Ireland

Somatostatin analogs (SSA) acting through SSTR2 like octreotide and lanreotide are a mainstay of acromegaly and neuroendocrine tumor treatment. Pasireotide, a newer compound acting mainly through SSTR5 and SSTR2, is used to treat Cushing disease and standard SSA-resistant acromegaly but has diabetogenic effects in animals and man. AP102 is a new SSA that has balanced sub-nanomolar affinity at SSTR2/SSTR5. We characterized the effect of AP102 versus pasireotide on glucose control in male ZDF rats, a standard diabetes model.

Diabetic ZDF rats were implanted with subcutaneous pumps containing AP102, pasireotide (3µg/kg/day) or vehicle, for 14 days. Fasting blood glucose was measured at baseline and on days 4 and 11. An oral glucose tolerance test (OGTT) was performed at baseline and on days 8 and 14. Water and food intake was measured daily.

All 3 groups were diabetic at baseline. Throughout the study the pasireotide group had significantly increased food and water intake as compared with vehicle and AP102 groups ($P<0.001$). AP102 did not differ from vehicle in terms of food/water intake, fasting glucose or OGTT responses. In contrast, pasireotide treated ZDF rats had significantly increased glucose AUC on OGTT as compared with vehicle ($p<0.05$) and AP102 ($p<0.01$) on day 14. There were no significant inter-group differences in terms of insulin, glucagon and GLP-1.

Unlike pasireotide, AP102 did not impair glucose control in diabetic rats, despite having high SSTR2/5 binding affinity. AP102 could represent a significant improvement over existing compounds if confirmed in human studies.

Adrian Daly is a consultant for Amryt Pharmaceuticals; Mark Sumeray is an Amryt Pharmaceuticals employee.

Volumetric Changes of Whole Brain Gray Matter and White Matter in Patients with Cushing Disease Using Voxel-Based Morphometry: A Prospective Study

Lu Gao[1,2*], Xiaopeng Guo[1,2*], Bo Hou[3], Xiaohai Liu[1,2], Kan Deng[1,2], Ming Feng[1,2], Xinjie Bao[1,2], Yong Yao[1,2], Wei Lian[1,2], Renzhi Wang[1,2], Bing Xing[1,2]

[*]These authors contributed equally to this work.

Department of Neurosurgery[1], China Pituitary Disease Registry Center[2], Department of Radiology[3], Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, P.R. China

Objective: The aim of the study was to prospectively assess the changes of whole brain gray matter and white matter volume in patients with Cushing disease using voxel-based morphometry (VBM). Besides, the correlation between abnormal brain volume and Scheltens score, Montreal Cognitive Assessment (MoCA) scale, course of disease and other possible risk factors were also evaluated. **Methods:** Twenty-one patients with Cushing disease, confirmed by pathology, were consecutive enrolled in the study from Peking Union Medical College Hospital. Nineteen sex and age matched healthy individuals were selected as controls. The whole brain three-dimensional structure imaging was evaluated using VBM method, which is based on satirical parametric mapping (SPM) 12 software. The whole brain gray matter and white matter volume differences between the two groups were analyzed accordingly. The Spearman rank test was used to analyze the correlation between abnormal brain volume and Scheltens, MoCA score and course of disease in patients with Cushing disease. This study was approved by the Ethical Committee of PUMCH. **Results:** Compared with control group, the cerebral gray matter volume was decreased in multiple regions in the group with Cushing disease. The changes in bilateral frontal lobe, temporal lobe and limbic lobe were statistically significant ($p < 0.05$). The atrophy volume of gray matter was positively correlated with the course of disease ($p < 0.05$) in certain cerebral regions, including left temporal lobe, superior temporal gyrus and temporal gyri. **Conclusion:** Our study confirmed the whole brain atrophy in patients with Cushing disease using VBM method. Quantitative analysis of the reduced gray matter volume demonstrated that the left temporal lobe atrophy volume and the course of disease were positively correlated. Thus, we should pay more attention to the early diagnosis and treatment of Cushing disease, in order to reduce the occurrence of severe brain atrophy.

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