Clinically non-functioning pituitary adenomas (NFPAs) represent the second most common subtype of pituitary tumours, representing 15–43% of all pituitary adenomas. NFPAs are usually benign tumours with no clinical evidence of hormonal hypersecretion. In most of the cases the tumours are arising from the gonadotroph lineage, but silent corticotroph, somatotroph, thyrotroph and rarely lactotroph cell characteristics can be discovered with immunostaining. As a result of lack of hormonal hyper-secretion, the diagnosis of NFPAs is made most often when the patient presents with mass effects due to a macroadenoma. NFPAs are most common tumour types in surgical series, and their primary treatment is indeed surgery. However, complete resection is achieved only in about 66% of the cases, and 20% of gross total resected tumours recur after 10 years.
Over the past few decades, remarkable progress has been achieved regarding medical treatment options for pituitary tumours. However, NFPAs remain the only subtype with no widely accepted pharmacological treatment. Dopamine receptor type 2 (DRD2) and somatostatin receptor (SST) expression have been demonstrated in NFPAs, prompting the investigation of dopamine agonists and somatostatin analogues as potential treatment strategies. The DRD2 agonist cabergoline is already used as first-line treatment of prolactinomas to induce tumour shrinkage and reduce prolactin secretion. Here we aim to investigate the efficacy of cabergoline on human NFPA tissue.

We assessed DRD2 expression levels via immunohistochemistry and qPCR in a large cohort of NFPAs (n=40) and in few prolactinomas (n=10). D2DR has two different isoforms, long (D2RL) and short (D2RS), which are differently expressed and can induce different effects on cell viability. In cabergoline-sensitive prolactinomas D2RS is the predominant isoform. NFPAs shown 10-fold and 5-fold decrease expression of D2RS and D2RL compared to prolactinomas, respectively. Additionally, in NFPAs we observed a significant decrease of cAMP production after cabergoline treatment (45% ±7; p<0.0001); however, viability after one-week cabergoline treatment showed only 4% (±0.7; p<0.0002) reduction, compared to a 10% decrease in prolactinomas (p<0.05). We also observed no difference in secretion of chromogranin A release in NFPAs upon treatment with cabergoline.

We have also seen in NFPAs downregulation of Gai2 protein expression levels, highlighting the general decrease of expression levels in the dopamine pathway (50% less, p<0.004).

Our data suggest that the difference in cabergoline responses between NFPAs and prolactinomas may be due to their distinct expression of D2DR isoforms, which differ by 29 amino acids in the third cytoplasmic loop, essential for G-protein binding. It has been shown that D2RL, but not D2RS, requires Gai2. The difference in D2R isoform expression could translate to distinct G-protein activation, ultimately leading to the contrasting viability results after cabergoline treatment. Taken together, these data will help inform future treatment strategies for patients with NFPAs.

Presentation: Monday, June 13, 2022 12:30 p.m. - 2:30 p.m.