

Studies on the diagnosis and treatment of canine Cushing's disease

Abstract of the Doctoral Thesis

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This study aimed to establish a magnetic resonance imaging–based classification system for canine Cushing’s disease, investigate somatostatin receptor (SSTR) and dopamine D2 receptor (DA2R) expression in canine adrenocorticotrophic hormone (ACTH)–secreting pituitary adenomas, and determine bone morphogenetic protein 4 (BMP4) and bone morphogenetic protein receptor (BMPR) expression in ACTH-secreting pituitary adenomas. In Europe and the USA, the usage of pasireotide, a somatostatin analog, was recently approved for the treatment of adult patients with Cushing’s disease for whom pituitary surgery is not a therapeutic option or has not been curative. Dopamine agonists are also reportedly effective for the treatment of Cushing’s disease in humans. Furthermore, bone morphogenetic protein 4 (BMP4) is reportedly associated with somatostatin analog action.

We developed a five-point classification system (Grades 1–5) based on tumor extension and classified as Type A and Type B according to the presence or absence of involvement of the arterial circle of Willis and cavernous sinus. According to this classification system, dogs with Type A, Grades 1–3 Cushing’s disease had a good prognosis following transsphenoidal hypophysectomy.

Furthermore, many cases of ACTH-secreting pituitary adenomas expressed SSTR2 and SSTR5, although more stained strongly positive for SSTR5 than SSTR2. On the other hand, there were few cases of DA2R expression. Therefore, somatostatin analogs and dopamine agonists may be useful for the treatment of Cushing’s disease in dogs according to immunohistological examinations of SSTR2, SSTR5, and DA2R in cases of incomplete resection or recurrence after surgery.

BMP4 and BMPRII were not expressed in ACTH-positive cells in normal canine pituitary tissue or ACTH-secreting pituitary adenomas. BMP4 is reportedly expressed in 30%–50% corticotrophic cells in the human pituitary gland. Therefore, we clarified that there is a species-specific difference in BMP4 expression in the pituitary gland. As reported by *in vitro* and *in vivo* studies, somatostatin analogs were effective in canine ACTH-secreting pituitary adenomas. However, considering our study findings, BMP4 signaling may not be an important factor

regarding somatostatin analog action.