学位論文内容の要旨
Abstract of the dissertation

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学位論文題名
The title of the doctoral dissertation

Steroid Profiling for assessing Adrenal Hepatic Syndrome in Canine Hepatocellular Carcinoma

（ステロイドプロファイリングによる肝細胞癌発症メカニズムとしての副腎–肝臓連関の探索）

Canine hyperadrenocorticism (HAC) is a common endocrine disorder with chronic overproduction of adrenocortical hormones. The clinicopathologic changes of liver such as elevated liver enzyme activities, steroid hepatopathy and glycogen accumulation in hepatic cells are frequently presented in dogs with HAC. Hepatocellular carcinoma (HCC) counts for 50-70 % of all primary hepatic tumors in dogs. It has been suggested that HCC is mostly occurred in dogs aged over 10 years and overpresented in male dogs. In our previous study, HAC was indicated as the highest concurrent disease of massive HCC. Furthermore, Scottish Terriers with vacuolar hepatopathy (VH) and steroid imbalance were also found to progress HCC. However, the exact mechanism of HAC and hepatocarcinogenesis are not well characterized in dogs.

To elucidate the involvement of HAC and HCC, the term ‘adrenal hepatic syndrome (AHS)’ was proposed in this study. AHS means chronic exposure of excess adrenal steroids and consequently makes the pathological changes in liver such as increased value of hepatic enzyme activities, hepatomegaly, hepatic vacuolation and hepatocellular injury. Similar phenomenon of AHS was occurred in dogs with HAC, changes of cortisol and other hormones are suggested to contribute the consequence clinicopathogenesis on liver. Therefore, this study aimed to quantify multiple serum steroids for accessing AHS in HCC.

In chapter 1, a simple analytical method using an automated column switching LC/MS/MS was developed and the impact of HAC on steroid profile was examined. The cortisol concentration

measured by ELISA was elevated than LC/MS/MS. In comparison of two methods, the study found the discrepancy between ELISA and LC/MS/MS. The findings showed that HAC impacted on steroid profile with elevated concentration of cortisone, 11-deoxycortisol and 17α-OH-progesterone in the baseline serum and, cortisol, cortisone, 11-deoxycortisol, corticosterone, 11-deoxycorticosterone and 17α-OH-progesterone in post-ACTH serum. Beside the cortisol, the additional five steroids were suggested to contribute the clinicopathogenesis of HAC.

In chapter 2, the differences in serum steroid profiles among HCC, HAC, and dogs with both diseases were investigated. Serum 19 steroids could be able to measure by conventional non derivatization and keto-derivatization method. None of steroids significantly differed among dogs with HCC, HAC or both diseases. The results indicated that steroidogenesis might not involve in the hepatocarcinogenesis and development of HCC.

Though steroid profile differences failed to prove the adrenal hepatic syndrome in HCC, the concurrent of HAC and HCC is evident. As a result, it is proposed that this interaction may also be affected by other confounding factors. Only information of steroids in serum was provided by this study. In the future, it may be useful to investigate the relationship between steroid imbalance and hepatocarcinogenesis by analyzing steroids and metabolites in liver tissues, and 24-hour urine. Additionally, follow up measurements of the steroid in those dogs could be helpful to determine whether steroid imbalance or hepatocarcinogenesis was presented first.