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学位論文内容の要旨

博士の専攻分野の名称：博士（獣医学）　　氏名：呉　南佶

学位論文題名

# A study on effects of non-steroidal anti-inflammatory drugs (NSAIDs) on differentiation capacity of canine osteogenic cells

（イヌ骨芽細胞の分化に対する非ステロイド性抗炎症薬の影響に関する研究）

Non-steroidal anti-inflammatory drugs (NSAIDs) have been used for pain management in orthopedic patients of animals as well as human beings with osteoarthritis or fracture. However, safety concerns for using NSAIDs in fracture patients have been remained as a controversy. Purpose of the present study was to evaluate effects of NSAIDs on differentiation capacity of canine osteogenic cells.

In Chapter 1, effects of short-term treatment with NSAIDs on osteogenic differentiation were estimated. Canine osteosarcoma cell line (POS) that could be spontaneously differentiated into osteoblastic cells were used for osteogenic model. During different stages of osteoblastic differentiation, POS cells were treated with carprofen and meloxicam for 72 hours. Morphological change of nodule formation, protein synthesis of alkaline phosphatase (ALP) and gene expressions of ALP and osteocalcin were evaluated in a time-course manner. Differentiation of osteoblasts was suppressed by NSAIDs in transitional stage between pre-osteoblastic and mature osteoblastic stages, which was correlated with delayed non-calcified nodule formation and decreased expression level of osteocalcin mRNA. However, fully calcified nodule formation was observed in all experimental groups during post-medication period. These results indicated that NSAIDs reversibly suppressed osteoblastic differentiation, which would have occurred by intrinsic potentials to restore insufficient $PGE_2$ in the cells.

In Chapter 2, to clearly demonstrate that compensatory responses to $PGE_2$ deficiency exist in normal ostegenic cells, canine bone marrow derived mesenchymal stem cells (BMSCs) were used. Osteogenic induction medium was supplemented with recombinant human interleukin (rhIL) -1β (1 ng/ml) as an inflammatory stimulator. Various classes of NSAIDs, including carprofen, meloxicam, indomethacin, and robenacoxib, were used to treat osteogenic cells during 20 days of osteogenic period in which matrix fully calcified. Levels of gene expressions were measured including osteoblast markers (ALP and osteocalcin), $PGE_2$ related enzymes (COX-1, COX-2, cPGES and mPGES-1) and $PGE_2$ receptors (EP2 and EP4). Levels of protein production levels of ALP, osteocalcin and $PGE_2$ were quantified. Morphologically, differentiation of ALP positive cells was observed and level of calcification was quantified. Decreased ALP expression and delayed differentiation into ALP positive cells by each of the NSAIDs were detected on day 4 when ALP expression was highest. Level of calcium deposition was

somewhat suppressed by NSAIDs on day 20, while osteocalcin production showed no significant suppression. Gene expression levels of $PGE_2$ related receptors and enzymes were up-regulated on day 4. Furthermore, levels of $PGE_2$ synthesis were restored at 48 hours under each of the NSAIDs. Channels for $PGE_2$ synthesis were utilized differently depending on the classes of NSAIDs, supported by differences in expression levels of EP2/EP4 and COX-1/COX-2 mRNA and in rates of $PGE_2$ restoration among the groups. These results indicated that intracellular compensatory responses occurred under $PGE_2$ deficiency derived by NSAIDs and inhibition of osteogenic differentiation would be more limited by using specific classes of NSAIDs.

In conclusion, canine osteogenic cells would have compensatory capacity to restore $PGE_2$ deficiency under NSAIDs treatment, which could prevent derailed osteogenic differentiation. Suppressive effects of NSAIDs on osteogenic differentiation would be minimal, suggesting that NSAIDs could be recommended for orthopedic patients as analgesics.