

糖尿病犬における運動の有用性および
運動と食事の時間的關係性について
(Evaluation of exercise in diabetic dogs and
temporal relationship between exercise and meal)

学位論文の内容の要旨

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医学領域において、運動療法は食事療法と共に糖尿病の基本治療である。運動は食事と組み合わせることで多彩な効果を発揮することが知られているが、食事内容や食事時間によっては運動時に低血糖や消化吸収不良などの弊害を引き起こすことが報告されており、両者の相互関係を把握することは重要と言える。本研究では、健常犬および糖尿病犬における食事と運動の時間的關係性を明らかにすると共に糖尿病犬に対する運動実施が、血糖コントロールに及ぼす影響を検討した。

結果より、糖尿病犬に対する 1 ヶ月間の継続運動は、糖尿病の長期コントロールマーカーである糖化アルブミン(GA)の有意な低下や、インスリンシグナリング(IRS-1, PI3-K, Akt2)や運動刺激により上昇し糖取り込みを亢進させる AMPK および GLUT4 発現量の上昇が認められ、血糖コントロールの改善に寄与することが明らかとなった。また、脂質代謝に関与している ACC や UCP3 の上昇、また NEFA の低下やアディポネクチンの上昇から運動刺激が脂質代謝改善および体脂肪の減少に寄与することが示された。

次に運動と食事の時間的關係性を検討するため、まず健常犬に対し糖給与下での運動および食後経過時間の異なる運動(食後 1-5 時間後)を実施した。結果、血中グルコースおよびインスリン濃度が高値を示す時間帯での運動や食後 1-4 時間経過後の運動は、血糖値の急激な低下を引き起こすことが明らかとなった。また食後 1-2 時間経過後の運動は血糖値の低下に加え、摂取した食物の消化吸収が遅延する傾向にあった。しかし、食後 5 時間経過後では、血糖値およびインスリン共に安定しており、血糖値の低下は起こらなかった。そこでこれらの結果を踏まえ、糖尿病犬に対し食後 6 時間および 8 時間での運動を実施した。糖尿病犬では、食後 6 時間が経過していたにも関わらず、血糖値の急激な低下が認められた。これは、健常犬が血糖値に反応してインスリン分泌を行うのに対し、糖尿病犬は外部からのインスリン投与により血糖値をコントロールしているためと考えられ、皮下から投与しているインスリン作用に大きく影響を受けることが明らかとなった。

本研究では、健常犬における運動療法の基準作製および糖尿病犬での運動の有用性を検討することができた。これらは今後、糖尿病犬に対する運動実施が有用な補助療法の 1 つとなり得る知見と考えられる。

Usefulness of exercise in diabetic dogs and temporal relationship between exercise and meals

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Exercise therapy as well as dietary therapy is one of the basic therapies for diabetic patients. In human study, primary effects of exercise therapy include improving blood glucose control, lipid metabolism and insulin sensitivity. Today, in patients with type 1 diabetes for whom exercise therapy is incorporated, correction of postprandial hyperglycemia and decrease in HbA1c, as well as effects of preventing complication and extending life expectancy have been reported, thus increasing significance of exercise therapy. On the other hand, depending on dosage of insulin or timing of mealtime, various side effects such as hypoglycemia or delayed digestion and absorption might be occurred in exercise therapy. However, effect of exercise therapy for glucose metabolism in dogs is not clear. Therefore, objective of this study was to determine usefulness of exercise in diabetic dogs and to elucidate relationship between exercise and meals.

The results showed that continuous one-month exercise in diabetic dogs significantly decreased GA level. Temporal analysis of postprandial glucose concentration after therapeutic exercises were tended to decreased. In regards to lipid metabolism, NEFA concentration was significantly decreased and adiponectin was elevated, suggesting decrease of body fat percentage owing to continuous exercise. AMPK and GLUT4 gene expression were elevated after one month exercise therapy respectively., suggesting glucose uptake by skeletal muscle in diabetic dogs. Furthermore, IRS-1, PI3-K, and AKT2 gene expression were elevated to 1.52, 1.73 and 1.5 times after exercise therapy, respectively, suggesting exercise therapy might induce up-regulation of insulin signaling pathway in diabetic dogs.

Changes in blood glucose concentration due to exercise therapy was reported to induce various side effects such as hypoglycemia and delayed digestion and absorption depending on dosage of insulin or timing of mealtime. Therefore the

purpose of this study was to investigate relationship between exercise therapy and mealtime. In Paragraph 1, we evaluated blood biochemical parameter before and after oral glucose tolerance test (OGTT) test in healthy 4 dogs. Exercise therapy was performed after 30 minutes of OGTT. The results suggested that exercise therapy induce decreasing blood glucose and insulin concentrations after OGTT. As such, conditions with both hyperglycemia and hyperinsulinemia have higher risk of lowering blood glucose concentrations. In the Paragraph 2, we studied influence of exercise performed with different time periods after a meal(1-5h) on glucose and lipid metabolism in healthy 4 dogs. The results showed that exercise therapy induced rapid decrease of blood glucose concentration in 1, 2, 3 and 4h after meals groups. However, 5h after meals group from exercise therapy was not observed any changes of blood glucose concentration, suggesting postprandial exercise with 5h after meals did not affect for blood glucose concentrations in healthy dogs. In Paragraph 3, we studied influence of exercise therapy performed with different time periods (6h and 8h after meals group) after a meal on glucose and lipid metabolism in 2 diabetic dogs. As a result, decrease of blood glucose concentrations, were observed in two diabetic dogs with 6h after meals. However, 8h after meals group from exercise therapy was not observed any changes of blood glucose concentration, suggesting postprandial exercise with 8h after meals did not affect for blood glucose concentrations in two diabetic dogs. Therefore, time period of exercise therapy might be better doing with 8h after meals.

The current study showed that the establishment a standard for exercise therapy in healthy dogs and its application for diabetic dogs. These evidences provide useful information for exercise therapy of diabetes mellitus in dogs.