Effect of Methylprednisolone Sodium Succinate on Innate Immune Function of Canine Peripheral Blood Phagocytes

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Abstract: Glucocorticoids (GCs) are the most widely used immunosuppressive agents, but animals treated with GCs may experience deleterious side effects which limit their use in many clinical conditions. In the present study, we examined whether methylprednisolone sodium succinate (MPSS), a glucocorticoid, modulates circulating leukocyte numbers, phagocytic capacity and oxidative burst activity (OBA) of canine peripheral blood phagocytes, and whether tumor necrosis factor-alpha (TNF-\(\alpha\)) release is affected by MPSS injection. Neutrophilia and monocytosis were induced by the administration of a high dose of MPSS, which is the recommended protocol for canine patients with acute spinal cord injury. The injection of MPSS decreased the phagocytic capacity of canine PMNs but not PBMCs, and recovered 12 hours (hr) after the completion of MPSS dosing. The OBA of both PMNs and PBMCs was suppressed by MPSS, and restored 24 hr after the completion of dosing. The lipopolysaccharide-induced TNF-\(\alpha\) release by PBMCs but not PMNs exposed to MPSS was reduced 12 hr after the completion of dosing, and recovered 48 hr after the completion of dosing. These results suggest that the application of MPSS protocol inhibits the innate immune functions of canine peripheral blood phagocytes for short time relatively.

Key words: Canine, Methylprednisolone sodium succinate, Phagocytic capacity, Oxidative burst activity, Tumor necrosis factor-\(\alpha\).

Introduction

Phagocytosis of innate immune cells such as neutrophils and monocytes is central in the elimination of most extracellular pathogenic foreign microbe (23). Phagocytosis is accompanied by diverse cellular processes such as engulfment, activation of microbial killing mechanisms, and production of cytokines (1,30). When phagocytes are activated by a variety of foreign particles, they are highly effective generating reactive oxygen species (ROS) by a process known as oxidative burst, following activation of a membrane associated nicotinamide adenine dinucleotide phosphate reduced (NADPH) oxidase (2). ROS derived from superoxide, together with proteases liberated from the granules, are used to kill ingested microbes. During infections, phagocytes represent a substantial source of cytokines such as tumor necrosis factor (TNF-\(\alpha\)) (4). Both neutrophils and monocytes have the ability to either express TNF-\(\alpha\) mRNA or secrete the related protein in vitro in response to lipopolysaccharide (LPS) (12). Those functions of phagocytes represent an important part of the host defense system against invading microorganisms.

Glucocorticoids (GCs) are the most widely used anti-inflammatory and/or immunosuppressive agents (26). However, animals treated with GCs may experience deleterious side effects which limit their use in many clinical conditions. GCs have an inhibitory effect on macrophage production of reactive oxygen molecules in rats (18,33). In vivo treatment with a single dose of cortisol or dexamethasone has been shown to cause reduced superoxide anion radical production in peripheral blood leukocytes (31). However, the contradictory results have been also reported. High doses of cortisone in vivo did not affect the phagocytic capacity and OBA of rabbit neutrophils (11). It has reported that increased neutrophil ingestion and killing capacity was induced by 6-methylprednisolone (28). A stimulatory effect of GCs on chemiluminescence of human monocytes has been also demonstrated (14).

Methylprednisolone sodium succinate (MPSS) is a glucocorticoid that has free radical-scavenging properties at very high dosages (7,15). In human medicine, it has been suggested that high dose treatment with MPSS is the only neuroprotective regime indicated by the results of the National Acute Spinal Cord Injury Studies (NASCIS) (5). Experimental evidence in cats with spinal cord injury (SCI) suggests that MPSS is useful in limiting the damaging effects of SCI (6). However, the use of MPSS in SCI remains controversial because of insufficient evidence to support the efficacy of MPSS in limiting SCI and the occurrence of immunosuppressive complications in healthy dogs that receive MPSS (20). Moreover, in the NASCIS II, humans who received MPSS had a 2.6-fold higher incidence of pneumonia (13).
The NACSIS I I I patients who received MPSS for 48 hours had a two-fold higher incidence of severe sepsis (19). Despite these side effects, the application of a high dose of MPSS has been prescribed for treatment of dogs with SCI.

In the present study, we examined whether MPSS modulates the phagocytic capacity, OBA and circulating number of canine peripheral blood phagocytes. In addition, we assessed whether LPS-induced TNF-α release from peripheral blood leukocytes is affected by MPSS injection.

Materials and Methods

Dogs

The subjects of this study were twelve 3-year-old healthy Beagle dogs. All dogs were kept in individual cages with a 12-hour light/dark cycle, and fed a commercial diet (ProPlan, Nestle Purina PetCare Korea Ltd, Seoul, Korea) and tap water. All experimental procedures and animal use were approved by the ethics committee of the Chungbuk National University.

Experimental protocol

The dogs were divided into two groups : dogs (n = 6) that received normal saline (control group) and dogs (n = 6) that received MPSS (SOLU-MEDROL INJ®, Pfizer Pharmaceuticals Korea, Seoul, Korea). The design of the experimental protocol involved the application of a high dose of MPSS, which is the recommended protocol for patients with acute SCI (39). The MPSS protocol started with an initial intravenous dose of 10 mg/kg of MPSS or normal saline. Peripheral blood drawn in heparinized tube from jugular vein was analyzed by an automated hematology analyzer, Cell-DYN 3500R (Abbott Diagnostics Division, Abbott Laboratories, Abbott Park, IL, USA) and finally adjusted to 1.077 specific gravity.