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Anti-Inflammatory Effect of Rice Protein in the Disease Initiated by the Spinal Cord Injury in the Rat Model

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Abstract

Background/Objectives: Treatments of inflammatory ailments of the central nervous system including diseases of an aging brain and of mood disorders are not satisfactory or non-existent despite a great and increasing demand. We performed a preclinical study to measure and characterize anti-neuroinflammatory activity unexpectedly associated with rice protein. **Methods:** Rice protein was administered orally continuously at 12-48 mg, 3 times per day to rats with the spinal cord injury (SCI) and the anti-neuroinflammatory effect measured by the standardized macrophage count in the cavity of injury (COI) test to determine a dose-dependent effect at 7 days post-SCI. The dose of 24 mg was used to characterize the macrophage-lowering effect from 7-56 days postSCI.**Results:** Rice protein had macrophage-lowering effect which was enhanced with increasing dose. The macrophage-lowering effect of the highest dose tested, 48 mg, was 45.6% vs 100% in untreated rats at 7 days post-SCI. Continuous administration of a dose of 24 mg for 56 days resulted in consistent reduction of macrophage counts.**Conclusions:** Oral administration of rice protein potently reduced severe, destructive inflammation initiated by SCI. Rice protein, as a GRAS (generally accepted as safe) food supplement may contribute to effective dietary management of ailments of the brain with inflammatory pathogenesis.

Keywords: rice protein; neuro-inflammation; aging brain; mood disorders; rat model of spinal cord injury; standardized macrophage count in the cavity of injury; anti-neuro-inflammatory effect; dietary supplement; dietary management of neuro-inflammation

1. Introduction

Treatments for neurotrauma, stroke, and neurodegenerative diseases of the central nervous system (CNS) are lacking or are generally not effective. This unfortunate status has not been helped by poor understanding of the pathogenesis of these diseases with futile therapeutic strategies aimed at wrong pathologic targets. Neurotrauma in the spinal cord injury (SCI) and in the traumatic brain injury (TBI) that results in a locally massive necrosis and hemorrhage in the white matter, initiate a severe and extraordinarily protracted inflammation fueled by large quantity of potently immunogenic damaged myelin [1]. The pathogenesis of this severe, destructive and extraordinarily protracted disease has recently been elucidated in a systematic study in the rat model of SCI where macrophage-rich infiltration is directed at removing myelin-rich necrotic debris and red blood cells and also associated with elevation of pro-inflammatory cytokines including IL-1b, IL-6 and IFN-g, and chemokines, and in damage to the spinal cord around the initial lesion [1,2].

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The progressively severe astrocytic response to neurotrauma and stroke is the most obvious cellular reaction associated with anti-inflammatory and anti-edema effect in the SCI [1,3] and while molecular mechanisms playing role in these beneficial functions currently are unknown, their effect on macrophage counts needs to be plotted in untreated animal models of neurotrauma and stroke against therapeutic effects related to experimental anti-inflammatory treatments until macrophages are eliminated from the site of injury [2,4]. This important parameter of preclinical studies on anti-inflammatory effect of experimental treatments has only recently been addressed [2,4,5].

Therapeutic strategies involving anti-inflammatory management have been considered in addressing neurodegeneration in an aging brain. Neuroinflammation involving activated, pro-inflammatory microglia and macrophages has been associated with neurodegeneration in progression of AD [6–9] and in mouse models of AD [10,11]. Despite failures of therapeutic strategies directed at removal of amyloid plaques and tau-rich neurofibrillary tangles (NF), more recent experimental anti-inflammatory treatments have been shown to inhibit the progression of cognitive decline and neuropathology in models of AD [12] and to reduce markers of neuroinflammation and of cognitive decline in clinical trials [13]. The frontal temporal dementia (FTD), a disease leading to cognitive decline and loss of cortical neurons but without deposition of amyloid and of NF, therefore of distinct pathogenesis from AD, has also been associated with neuroinflammation involving activated microglia and pro-inflammatory macrophages [14–16]. Neurodegeneration in Parkinson's disease (PD) has been associated with neuroinflammation involving activated microglia and pro-inflammatory macrophages with neuroinflammation resulting from a preceding TBI or stroke considered a highly contributing factor [16–20]. The pathogenesis of amyotrophic lateral sclerosis (ALS) involves a rapid degeneration of spinal motor neurons and specific neurons in the brain cortex and subcortical nuclei integrated in the motor function. The neuroinflammation with activation of microglia and infiltration by pro-inflammatory macrophages in the spinal and cerebral areas has been documented in human patients [15,21–23] and in SOD-1 mouse mutants [24–27].

Immune-mediated myeloencephalitides, inflammatory diseases of the spinal cord and the brain include multiple sclerosis (MS), and neuromyelitis optica (NMO). While specific antigens against which immune reaction is mounted are still unknown in MS, auto-antibodies directed against the aquaporin-4, a water channel in astrocytic cell membrane initiate a severe, rapidly progressing NMO. Although some forms of early MS involve perivascular inflammation that recedes after a period of time, chronic MS tends to result in a more severe, parenchymal inflammation that involves activated microglia and pro-inflammatory macrophages active in demyelinating plaques [28–31]. Immunosuppressive treatments of MS have been used with variable, often inadequate outcomes. Mood disorders including major depressive disorder [32–34] and bipolar disorder [35–37] have chronic neuroinflammatory pathogenesis.

The inhibition and elimination of the severe inflammation initiated by SCI in the rat model has recently been accomplished with oral administration of xanthohumol [2] indicating that this plant-derived flavonoid with excellent safety profile [38] should be considered in treatment of neuroinflammation.

Rice protein constitutes 10% of the brown rice content and is obtained by plant enzymatic hydrolysis. Rice protein typically contains 80% of glutelin and 10% globulin that are insoluble in water [39] and greater degree of hydrolysis makes them more water soluble. Commercially available rice protein typically contains a mixture of low molecular weight peptides and amino-acids with notable deficiency of 3 essential amino-acids: lysin, threonine and tryptophane requiring supplementation. Otherwise, rice protein has low immunogenicity, has been used as an effective substitute to whey protein in infant formula for babies allergic to cow milk [39,40] and is widely used in oral drug formulations and in dietary supplements. While therapeutically beneficial effects of rice protein still need to be further explored, fractions of rice bran, a distinct product of rice grain milling process, have potent anti-oxidant activity with anti-diabetic effects [41], lowering hypertension [41,42] and also inhibiting vascular pathologies in atherogenic rat and mouse models [43–46]. In a chronic feeding study involving aged NMR mice, rice bran supplementation improved cognition, survival and function of brain mitochondria [47] confirming its transmission of anti-oxidative effects via the blood brain barrier and indicating neuroprotective activity associated with rice bran. Rice bran is not water soluble and its taste is unfavorable.

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In this study, we detected and investigated anti-neuroinflammatory effect of rice protein administered orally to rats after the SCI. Rice protein lowered counts of macrophages in the cavity of injury (COI) which was dose-dependent and accelerated the elimination of macrophages from the COI. Given very common and widespread consumption of rice, rice protein a GRAS (generally accepted as safe) food supplement [48] should be considered in dietary management of common neurodegenerative ailments of aging brain and in mood disorders with neuroinflammatory pathogenesis.

2. Materials and Methods

Animal experiments were conducted after the approval by the Animal Research Ethics Board at McMaster University along the guidance by the Canadian Council of Animal Care.

The spinal cord injury model in the rat.

Healthy male Long Evans rats aged 12 weeks, 340-390 g, were offered a fruit (strawberry or raspberry) flavored jello cube once a day, for 1 week prior to the surgery and were separated in individual cages 3 days before the surgery. Rats were induced with 5% isoflurane in 95% oxygen flowing at a rate of 1 liter per minute and maintained at 3.5% isoflurane in 96.5% oxygen. The anaesthetized rats had skin on the back shaved and prepared for surgery with 70% ethyl alcohol and 10% iodine swabs. The skin was cut open over the caudal thoracic and lumbar spine and spinal muscles dissected from the vertebral spine of the thoracic 10 (T10) vertebrum and the dorsal arches of this vertebrum removed. A 3Fogarty catheter was inserted via this laminectomy over the intact dura towards the head to place the caudal edge of the 3 mm long balloon at 1 cm rostral to the laminectomy. The balloon was inflated with 15 µL of sterile saline for 3 minutes, then deflated and the catheter removed. The spinal muscles were closed with absorbable sutures over the laminectomy and the skin incision was closed with nylon non-absorbable sutures. Before awakening, the rats were administered; 50 µL of a painkiller, ketoprofen, 100mg/mL, (Merial) subcutaneously, and 50 µL of antibiotic, enrofloxacin 50 mg/mL (Bayer) intramuscular, and 3 mL of saline subcutaneous.

Treatments.

The fruit jello cubes were prepared by diluting the jello powder, in post-boiling water and poured at 5 mL into plastic cube forms, then let to set in the refrigerator at 4°C.

Brown rice protein (CONVENTIONAL ORYZATEIN® SILK 90, AXIOM Foods, Los Angeles, CA, U.S.A.) was suspended in cold tap water and then added to liquid native jello to obtain a content of 12 - 48 mg of rice protein per 5 mL jello cube. The jello cubes were left to set in the refrigerator at 4°C.

Immediately after waking up from the anaesthesia post-SCI surgery, rats were offered a jello cube and then every 8 hours for 7-56 days days. The ingestion of all jello cubes was noted to occur in all study rats after the surgery.

Endpoint.

Given the invasive nature of the SCI model, an ethical Endpoint was instituted. A rat with distended urinary bladder that was impossible to express or was ruptured, or with severe dehydration and with hypothermia and lethargy, was humanely euthanized and not used in the study. The rats were administered the painkiller once daily for 2 days post-surgery and rats with distended urinary bladder and blood in urine were given the antibiotic once daily for 5 days post-surgery. Rats with moderate dehydration were administered with 5-10 mL saline subcutaneously once or twice a day as needed. Every day until the normal bladder function returned and micturition stopped, rats with distended urinary bladder and micturition resulting in soiling of the perineal area had the bladder gently manually expressed once or twice a day and had a bath of the hind end in warm clean tap water followed by blotting of a wet hind end with paper towels.

Pathology.

The SCI rats were overdosed with the sodium pentobarbital (80 mg/kg b.w.) administered intraperitoneally. When in deep plane of anaesthesia, the chest was cut open, 100 international units of heparin sodium injected into the left heart ventricle and a cannula with flowing lactated Ringer's solution inserted into the left ventricle while the right auricle was cut open. After the blood was washed out, the flow of the lactated Ringer's solution was replaced by that of phosphate buffered formalin and the carcass

 doi:10.20944/preprints202604.1652.v1

was fixed. The spine was removed, postfixed in formalin overnight and then placed in formalin supplemented with 8%EDTA, pH 7.0, to decalcify the spinal vertebrae. The decalcifying solution was replaced by fresh one every 2 days for 2 weeks. Once soft, the spine was cut perpendicular to its long axis into 3 mm thick segments consecutively starting from laminectomy rostrally to include the SCI lesion. Eight segments were processed in rising concentrations of ethyl alcohol and xylene, embedded in paraffin wax, cut 5 μm thick and mounted on the glass slide. The sections were stained with luxol fast blue and counterstained with hematoxylin and eosin (LFB+H&E) and cover slipped. Stained sections were examined by an experienced experimental neuropathologist (the first author) under a Nikon Eclipse 50i light microscope. At 40x magnification a margin of one COI per section, including 20% of the spinal cord and 80% of the COI was digitally photographed at 40x magnification. The images were then analyzed and macrophages; large cells with a round, oval, sometimes subcleaved nucleus with abundant cytoplasm containing blue granules of myelin debris and/or red blood cells [1,2,4], were counted. The counts were averaged for a rat and these averages averaged for a treatment group.

Statistical Analysis

Quantitative data generated by the standardized macrophage count in the COI were analyzed by Student T-test.

3. Results

Results of this study on the anti-inflammatory effect of rice protein and/or xanthohumol administered orally to rats with the SCI are demonstrated in Figures 1 and 2.

Oral administration of rice protein 3 times per day for 7-56 days had an anti-inflammatory effect of lowering the numbers of macrophages in the COI (Figure 1) with apparent reduction of the loss of volume of peri-lesional spinal cord and inhibition of the enlargement of the COI similar to the anti-inflammatory effect of xanthohumol [2].

Fig. 1. Histology of spinal cord injury in the rat model 28 days post-trauma.

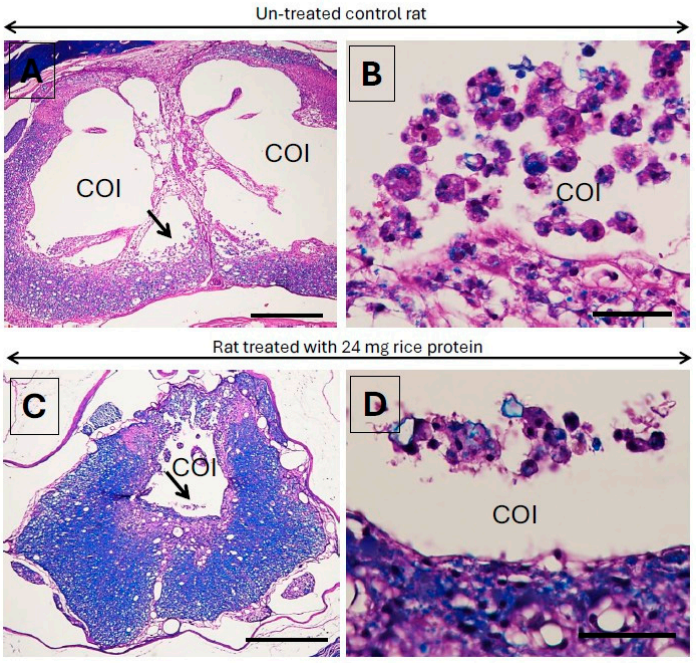


Figure 1. LEGEND: In an untreated rat 28 days post-SCI the cavity of injury (COI) is markedly distended with clear fluid and contains numerous large phagocytic macrophages (area indicated by arrow in A, C) laden with blue granules of myelin debris (A, B). In a rat dosed with rice protein the COI is remarkably smaller and contains

 doi:10.20944/preprints202604.1652.v1

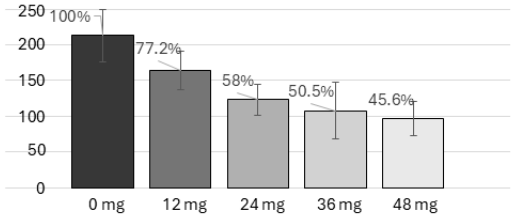
fewer phagocytic macrophages (C, D). A small arrow in A and C indicates the area magnified in B, D. Luxol fast blue counterstained with hematoxylin and eosin (LFB+H&E). Size Bars: 500 mm in A, C. 50 mm in B, D.

The standardized macrophage count in the COI test [2,4] performed in the injured spinal cord at day 7 post-SCI allowed for accurate determination of anti-inflammatory activity of raising doses of rice protein from 12 – 46 mg (Figure 2A). While the average number of macrophages in the COI of untreated SCI rats was expressed as 100%, administration of rice protein at 12 -48 mg/dose resulted in corresponding gradual reduction of macrophages from 77.2% to 45.6% (Figure 1A) demonstrating a direct and accurate relationship between the dose of rice protein and its anti-neuroinflammatory effect.

To determine the macrophage-lowering effect of continuous rice protein administration on the inflammatory disease initiated by SCI in the rat model, a dose of 24 mg, 3 times per day was administered orally for 7-56 days. Untreated rats served as controls. While the numbers of macrophages in the COI of untreated rats declined rapidly after day 7 post-SCI and this decline slowed to a more gradual after day 28 (Figure 2B) indicating natural anti-inflammatory mechanisms in the spinal cord attributed to astrogliosis [1,2,5], rice protein-dosed rats had consistently greater reduction in counts of macrophages from day 7-56 with almost complete elimination of macrophages on day 56 (Figure 1B). Statistical analysis of this macrophage-lowering effect by rice protein revealed significant effect at days 7, 14 and 56 post-SCI but not at days 28 and 42 post-SCI.

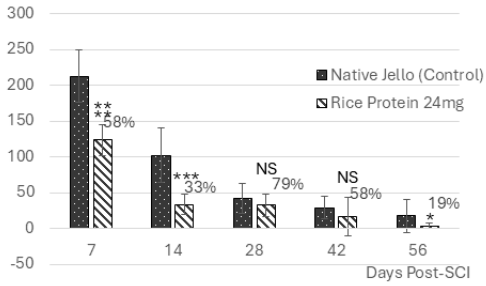
Fig. 2. Anti-inflammatory effect of rice protein in disease initiated by the spinal cord in jury in the rat model.

Fig. 2A. Macrophage-lowering activity in the cavity of injury (COI) by rice protein at 7 days post-trauma.



LEGEND: SCI rats were dosed 3x per day with 0-48 mg rice protein. While the average counts of macrophages in the COI are expressed as 100%, counts in rats administered with raising doses of rice protein was reduced in corresponding fashion, reaching 45.6% at the highest dose tested at 48 mg. T-test $p<0.005$.

Fig. 2B. Dose effect of 24 mg of rice protein per dose on macrophage-lowering activity in COI from day 7-56 post-trauma.



LEGEND: SCI rats were dosed 3x per day with 24 mg rice protein continuously for 56 days. The dark columns show average of macrophage counts at 7-56 days and are 100% at each time point. The adjacent light columns show reduced averages of macrophages with indication of % of macrophages vs controls at each time point. Differences in average macrophage counts were analyzed for each time point with T-test. For 7 days post-SCI $p<0.00002$, for 14 days $p<0.0003$, for 28 days $p=0.174$, for 42 days $p=0.021$, for 56 days $p<0.03$.

Figure 2.

 doi:10.20944/preprints202604.1652.v1

4. Discussion

This study demonstrates that oral administration of brown rice protein resulted in an anti-neuroinflammatory effect that inhibited severe inflammatory disease initiated by the spinal cord injury (SCI) and accelerated its elimination.

The anti-neuroinflammatory effect of brown rice protein was measured by reduction of macrophage counts in the cavity of injury (COI) in the SCI rat model. This emerging quantitative histologic test has been developed previously in the rat model of the SCI [2,4]. It allows for accurate determination of anti-inflammatory effect by agents that cross the blood-spinal cord barrier (BSCB) such as xanthoumol [2]. By using this test in the present study, we determined the macrophage-lowering effect of 72.2-45.6% vs untreated controls (100%) by increasing doses of rice protein from 12-48 mg. The reduction to 45.6% in macrophage numbers is remarkable and comparable to the macrophage-lowering effect by optimal dose of hop xanthohumol in a recent rat study [Kwiecien et al, manuscript in preparation]. To determine the long-term anti-inflammatory effect of a dose of rice protein administered continuously we used 24 mg/dose for 56 days, the period of time previously shown to be sufficient to eliminate macrophages from the COI by other effective anti-inflammatory treatments, Serp-1 [4] and xanthohumol [2]. The continuous oral dosing with rice protein consistently reduced numbers of macrophages in the COI when compared with untreated controls from day 7- 56 post-SCI (Figure 2B). This effect was statistically significant at 7, 14 and 56 days but not at 28 and 42 days post-SCI. While changes in locomotor function in all SCI rats were recorded in this study, the results were not accurate enough to independently detect changes in therapeutic effect of increasing doses of rice protein and are not provided nor discussed.

Brown rice protein constitutes 10% of the content of the rice grain and it is a mixture of small proteins, peptides and amino acids with excellent nutritional characteristics extracted by hydrolysis involving plant enzymes [40,49]. In a recent study a Rice 14 peptide isolated from leaves of wild rice (*Oryza minuta*) was found to have anti-inflammatory activity in vitro by inhibiting secretion of IL-1b from macrophages activated by gout-derived monosodium urate crystals [50]. While studies on anti-inflammatory activity in rice protein are generally lacking, rice bran separated in a milling process contains a mixture of bio-active phytosterols, tocotrienols, tocopherols, flavonoids, and phenolic molecules with antioxidant, anti-inflammatory, and antimicrobial activities [51–53]. The use of rice bran has been shown to be protective for mitochondria [54], particularly important as neuroprotective effect in Alzheimer's disease but anti-neuroinflammatory activity of rice protein is less certain. The milling process and hydrolysis used to extract rice protein makes it a distinct portion of grain rice from its bran.

In needs to be pointed out that the spinal cord itself has an anti-inflammatory activity that consistently lowered macrophage counts in the COI. While the molecular identity of this novel activity still needs elucidation, it appears to be increasing in effectiveness after day 7 post-SCI and may be related to progressively increasing severity of astrogliosis in the spinal cord around the COI [1,2,5]. In a previous study, inflammation initiated by SCI in the adult severely dysmyelinated Long Evans Shaker (LES) rat, a mutant of myelin basic protein gene [55] was completely eliminated from the COI before day 7 post-SCI [56]. Such potent anti-inflammatory activity is related to severe, generalized astrogliosis developing in the LES rat due to the lack of myelin sheaths [55]. This intrinsic anti-inflammatory activity is a fundamental factor in the pathogenesis of disease initiated by the SCI [1] and by traumatic brain injury (TBI), concussion and by stroke [2]. It needs to be considered in preclinical analyses of candidate anti-neuroinflammatory agents.

Given the physical character of rice protein, a mixture of small proteins, peptides and amino acids, this hydrolysate extract from rice grain may not be a good treatment of an inflammatory disease considering the regulatory requirements which demand rigorous efficacy and safety testing of individual candidate therapeutic molecules. However, rice protein is GRAS (generally accepted as safe) [48] and very widely consumed therefore, as a food supplement with appropriate dosing guidelines it may serve as an effective inhibitor of neuroinflammation in neurodegenerative diseases

 doi:10.20944/preprints202604.1652.v1

of aging brain of growing concern to aging population as well as in mood disorders with inflammatory pathogenesis.

5. Conclusions

Oral administration of rice protein potently reduced severe, destructive inflammation initiated by SCI. The anti-inflammatory effect of 48 mg, the highest dose tested, was comparable to the effect of the optimal dose of hop xanthohumol, the first effective treatment of disease initiated by the SCI. The standardized macrophage count in the COI has been confirmed as an accurate test to measure the anti-neuroinflammatory activity of candidate treatments. Rice protein, as a GRAS (generally accepted as safe) food supplement may contribute to effective dietary management of ailments of the brain with inflammatory pathogenesis.

6. Patents

WO 2026/036211 A1, PCT/CA2025/051062, US-2026-0048095-A1.

Author Contributions: JMK: conceptualization, methodology, investigation, resources, writing – original draft preparation, writing – review and editing, visualization, supervision, project administration. ; WD: review and editing, clinical input.; BJ K-D: methodology, investigation.; CJ K-D: validation, formal analysis, data curation.; KHD: supervision, funding acquisition.

Funding: Provided by VPC NeuroPath CONSULTING, Inc.

Institutional Review Board Statement: The animal studies have been approved by the Animal Ethics Research Board at McMaster University, Hamilton, ON, Canada under the Animal Use Protocol 23-23.

Informed Consent Statement: None.

Data Availability Statement: Archived histologic slides and microphotographs available upon request from Dr. JM Kwiecien, kwiecien@mcmaster.ca.

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Conflicts of Interest: JMK and KHD are partners in VPC NeuroPath CONSULTING, Inc., that provided funding for this study.

Abbreviations

The following abbreviations are used in this manuscript:

BSCB	blood spinal cord barrier
CNS	central nervous system
COI	cavity of injury
SCI	spinal cord injury
LES	Long Evan Shaker (rat)

 doi:10.20944/preprints202604.1652.v1

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