UNIVERSITI PUTRA MALAYSIA

HOST CELL RESPONSE IN MICE FOLLOWING ORAL INOCULATION WITH DIFFERENT DOSES OF PASTEURELLA MULTOCIDA TYPE B: 2 AND ITS LIPOPOLYSACCHARIDES

OMAR SUWAIDAN ALI

FPV 2015 6

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By

OMAR SUWAIDAN ALI

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Master of Veterinary Science

March 2015

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DEDICATIONS

To

MY ALLAH

My beloved parents, my beloved brothers and sisters and special dedication to the friend and my senior teacher Dr. Lawan Adamao from Nigeria in giving my moral supports that helped me countless time to overcome each and every obstacles.

Thank you to those people who have guided and inspired me throughout my journey of education.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in Fulfillment of the requirement for the degree of Master of Veterinary Science

HOST CELL RESPONSES IN MICE FOLLOWING ORAL INOCULATION WITH GRADED DOSES OF *PASTEURELLA MULTOCIDA* TYPE B: 2 AND ITS LIPOPOLYSACCHARIDES

By

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March 2015

Chair: Faez Firdaus Jesse Abdullah, Ph.D.
Faculty: Veterinary Medicine

Haemorrhagic septicaemia (HS) is an infectious disease of cattle and buffalo inflicted by serotypes B: 2 and E: 2 of *Pasteurella multocida* in Asian and African countries respectively. This study was carried out to study the possibility of using the extracted LPS from *Pasteurella multocida* type B: 2 to use it in the future to produce oral vaccine against HS in cattle and water buffaloes. Therefore, the present study aims at evaluating the host cell responses in Balb c mice after 120 hours post inoculation with graded doses of *Pasteurella multocida* type B: 2 and its LPS via oral route of inoculation. Sixty healthy Balb c mice of eight to ten weeks old of both sexes were enrolled in this study. The animals were confirmed negative for *Pasteurella multocida* type B: 2 following culture of peripheral blood for bacterial isolations. The mice were housed in plastic cages and provided with water and pellet ad libitum. Sixty healthy Balb c mice were placed in twelve plastic cages each one containing five mice. Throughout the experiments, two types of inoculums were used; the whole cell of *Pasteurella multocida* type B: 2 and its lipopolysaccharide (LPS) extracted from the bacteria. The mice were divided into three major groups (A, B and C). Group A is the control group (n = 10) and were inoculated with 0.4 ml of PBS pH 7.4 orally. The treatment groups (B; n = 25 and C; n = 25) were inoculated with 0.4 ml of *Pasteurella multocida* type B: 2 and its lipopolysaccharide respectively. The mice in group B and C were further divided into five subgroups. The subgroups were designated based on the graded doses as $B10^1$, $B10^3$, $B10^5$, $B10^7$ and $B10^9$ for *Pasteurella multocida* type B: 2 and $C10^1$, $C10^3$, $C10^5$, $C10^7$ and $C10^9$ for LPS respectively. The mice were observed for clinical signs and mortality rates after inoculation for 120 hours. Mice that showed severe clinical signs and survived mice after 120 hours post-inoculation were sacrificed via cervical dislocation approach and post-mortem examination was performed. Blood samples were collected directly from the heart into plain and EDTA tubes for the analysis of acute phase protein concentration (Serum amyloid A (SAA) and Haptoglobin (Hp), Cytokines concentration (Interleukin-1β (IL-1β) and Interleukin-6 (IL-6)) and the hematological parameters. Post mortem was conducted and the intestine, kidney, spleen, lungs and liver were sampled for histopathological study. The concentration of SAA was significantly higher ($p < 0.001$) in the $B10^9$ cfu of *Pasteurella multocida* type B: 2 and $C10^9$ cfu of LPS compared to the control group and the other treatment groups. The concentration of Hp was significantly higher ($p< 0.001$) in the $B10^9$ of *Pasteurella multocida* type B: 2 and $C10^9$ of LPS compared to the control group and the other treatment groups. The concentration of IL-1β was significantly higher ($p < 0.001$) in the $B10^7$ of *Pasteurella multocida* type B: 2 and $C10^9$ of LPS compared to the control group and the other treatment groups. The

concentration of IL-6 was significantly higher ($p< 0.001$) in the $B10^3$ cfu of *Pasteurella multocida* type B: 2 and $C10^9$ cfu of LPS compared to the control group and the other treatment groups. The clinical signs (ruffled fur, ocular discharges level of alertness and laboured breathing) were significantly higher ($p<0.001$) in the mice inoculated orally with $B10^9$ and $C10^9$ cfu of *Pasteurella multocida* type B: 2 and its LPS respectively. RBC, PCV, haemoglobin concentrations (Hb), WBC, Lymphocytes and monocytes significantly decreased ($p < 0.0001$) in mice inoculated with 10^9 cfu of *Pasteurella multocida* type B: 2 and its LPS. Prothrombin time (PT), activated partial thromboplastin time (APTT), thrombocyte, eosinophils, plasma proteins, band and segmented neutrophils significantly increased ($p < 0.0001$) in mice inoculated with $B10^9$ cfu of *Pasteurella multocida* type B: 2 and its LPS. Congestion was significantly higher ($p < 0.0001$) in the lungs and spleen of the mice inoculated with $B10^9$ cfu of *Pasteurella multocida* type B: 2. Inflammatory cells were significantly higher ($p < 0.0001$) in the intestines and liver of the mice inoculated with $B10^9$ cfu of *Pasteurella multocida* type B: 2. Furthermore, degeneration and necrosis were significantly higher ($p < 0.0001$) in the kidney of the mice inoculated with $B10^9$ cfu of *Pasteurella multocida* type B: 2. Congestion was significantly higher ($p < 0.0001$) in the lungs, spleen and liver of the mice inoculated with $C10^9$ cfu of LPS. Inflammatory cells were significantly higher ($p < 0.0001$) in the intestines of the mice inoculated with $C10^9$ cfu of LPS. Furthermore, degeneration and necrosis were significantly higher ($p < 0.0001$) in the kidney of the mice inoculated with $C10^9$ cfu of LPS. In conclusion, this model could be used to enhance the understanding of the progression of Haemorrhagic septicaemia (HS) disease following graded doses infection via oral route.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Sarjana Sains Veterinar

TINDAKBALAS SEL PERUMAH DALAM MENCIT BERIKUT INOKULASI LISAN DENGAN DOS YANG BERBEZA BAGI *PASTEURELLA MULTOCIDA* JENIS B: 2 DAN LIPOPOLISAKARIDANYA

Oleh

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Hawar berdarah (HS) merupakan penyakit berjangkit lembu dan kerbau yang disebabkan oleh *Pasteurella multocida* serotaip B: 2 dan E: 2 di negara-negara Asia dan Afrika masing-masing. Tujuan kajian ini adalah untuk menilai tindakbalas sel perumah dalam mencit Balb c selepas 120 jam berikutan inokulasi dengan dos berbeza bagi *Pasteurella multocida* jenis B: 2 dan LPSnya melalui inokulasi laluan lisan. Enam puluh mencit Balb c yang berumur diantara lapan hingga sepuluh minggu yang terdiri daripada kedua-dua jantina digunakan dalam kajian ini. Haiwan-haiwan telah disahkan negatif untuk *Pasteurella multocida* jenis B: 2 daripada sampel darah periferi bagi tujuan analisis bakteria. Kesemua mencit tersebut di tempat kah di dalam plastik sangkar dan air dan pellet telah disediakan sepanjang masa. Enam puluh ekor mencit telah diasingkan dalam dua belas sangkar plastik dengan setiap satu sangkar dengan lima ekor mencit. Sepanjang eksperimen, dua jenis inokulum telah digunakan; keseluruhan sel *Pasteurella multocida* jenis B: 2 dan lipopolisakaridanya (LPS) yang diekstrak daripada bakteria. kesemua mencit tersebut dibahagikan kepada tiga kumpulan utama (A, B dan C). Kumpulan A adalah kumpulan kawalan (n = 10) dan telah disuntik dengan 0.4 ml PBS pH 7.4 secara lisan. Kumpulan-kumpulan rawatan (B; n = 25 dan C; n = 25) diinokulasi dengan *Pasteurella multocida* Jenis B: 2 dan lipopolisakaridanya masing-masing. Mencit dalam kumpulan B dan C telah dibahagikan kepada lima kumpulan kecil. Subkumpulan telah ditetapkan berdasarkan dos berbeza seperti $B10^1$, $B10^3$, $B10^5$, $B10^7$ dan $B10^9$ untuk *Pasteurella multocida* jenis B: 2 dan $C10^1$, $C10^3$, $C10^5$, $C10^7$ dan $C10^9$ untuk kumpulan LPSnya. Kesemua mencit tersebut telah diperhatikan tanda-tanda klinikal dan kadar kematian selepas inokulasi selama 120 jam. Mencit yang menunjukkan tanda-tanda klinikal yang teruk dan tikus yang hidup selepas 120 jam inokulasi dikorbankan melalui pendekatan dislokasi leher dan pemeriksaan bedah siasat dilakukan. Sampel darah diambil secara langsung daripada jantung ke dalam tiub darah biasa dan EDTA untuk analisis kepekatan protein fasa akut (Serum amiloid A (SAA) dan haptoglobin (Hp), konsentrasi sitokin (Interleukin-1β (IL-1β) dan Interleukin-6 (IL-6)) dan data-data hematologi. Bedah siasat telah dijalankan dan usus, buah pinggang, limpa, paru-paru dan hati telah disampel untuk kajian histopatologi. Kepekatan SAA nyata lebih tinggi ($p < 0.001$) bagi kumpulah $B10^9$ cfu *Pasteurella multocida* jenis B: 2 dan $C10^9$ LPSnya berbanding dengan kumpulan kawalan dan kumpulan rawatan lain. Kepekatan Hp nyata lebih tinggi ($p < 0.001$) dalam kumpulan $B10^9$ *Pasteurella multocida* jenis B: 2 dan kumpulan $C10^9$ LPSnya berbanding. Kumpulan Kawalan dan kumpulan rawatan lain. Kepekatan IL-1β nyata lebih tinggi ($p < 0.001$) dalam kumpulan $B10^7$ *Pasteurella multocida* jenis B: 2 dan kumpulan $C10^9$ LPSnya berbanding dengan kumpulan kawalan dan kumpulan rawatan lain. Kepekatan

IL-6 nyata lebih tinggi ($p < 0.001$) dalam kumpulan $B10^3$ yang *Pasteurella multocida* jenis B: 2 dan kumpulan $C10^9$ cfu LPSnya berbanding dengan kumpulan kawalan dan kumpulan rawatan lain. Tanda-tanda klinikal (bulu tegak, tahap pelepasan mata kewaspadaan dan kadar pernafasan) jauh lebih tinggi ($p < 0.001$) pada kumpulan $B10^9$ dan $C10^9$ cfu *Pasteurella multocida* jenis B: 2 dan LPSnya masing-masing. RBC, PCV, kepekatan hemoglobin (Hb), WBC, Limfosit dan monosit telah menurun secara signifikan ($p < 0.0001$) pada kumpulan disuntik dengan 10^9 cfu *Pasteurella multocida* jenis B: 2 dan LPSnya. Masa prothrombin (PT), diaktifkan separa masa tromboplastin (APTT), trombosit, eosinofil, protein plasma, band dan neutrofil bersegmen telah meningkat secara signifikan ($p < 0.0001$) pada kumpulan disuntik dengan $B10^9$ cfu *Pasteurella multocida* jenis B: 2 dan LPSnya. Kesesakan nyata lebih tinggi ($p < 0.0001$) dalam paru-paru dan limpa kumpulan yang disuntik dengan $B10^9$ cfu *Pasteurella multocida* jenis B: 2. Sel radang nyata lebih tinggi ($p < 0.0001$) dalam usus dan hati kumpulan mencit yang disuntik dengan $B10^9$ cfu *Pasteurella multocida* jenis B: 2. Selain itu, degenerasi dan nekrosis secara signifikan lebih tinggi ($p < 0.0001$) dalam buah pinggang kumpulan mencit disuntik dengan $B10^9$ cfu *Pasteurella multocida* jenis B: 2. Kesesakan nyata lebih tinggi ($p < 0.0001$) dalam paru-paru, limpa dan hati kumpulan mencit yang disuntik dengan $C10^9$ cfu LPS. Sel-sel inflamasi adalah lebih tinggi ($p < 0.0001$) dalam usus kumpulan mencit disuntik dengan $C10^9$ cfu LPSnya. Tambahan pula, degenerasi dan nekrosis secara signifikan lebih tinggi ($p < 0.0001$) dalam buah pinggang kumpulan mencit disuntik dengan $C10^9$ cfu LPSnya. Kesimpulannya, model ini boleh digunakan untuk meningkatkan pemahaman tentang perkembangan penyakit hawar berdarah dengan jangkitan dos yang berbeza melalui laluan lisan.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Master of Veterinary Medicine.

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LIST OF ABBREVIATIONS/ NOTATIONS/ GLOSSARY OF TERMS

%	Percentage
°C	Degree Celsius
µg	microgram
µl	microliter
APP	Acute phase proteins
APR	Acute phase reaction
BHI	Brain Heart Infusion
cfu	colony forming unit
ELISA	Enzyme Linked Immunosorbent Assay
Hp	Haptoglobin
HS	Haemorrhagic septicemia
ICR	Institute of Cancer Research
min	minute
PBS	Phosphate Buffered Saline
SAA	serum amyloid A
VRI	Veterinary Research Institute
PT	Prothrombin time
APTT	activated partial thromboplastin time
LPS	Lipopolysaccharide
P.M.	Pasteurella multocida
IL-1β	Interleukins-1β
IL-6	Interleukins-6
TMB-Substrate	3, 3', 5, 5'-Tetramethylbenzidine Liquid Substrate

HRP-aviden	Horse Radish Peroxidase Avidin
nm	Nanometers
pg	Picogram
rpm	Revolutions per minute
s	second

CHAPTER 1

INTRODUCTION

The Gram-negative bacterium *Pasteurella multocida* is of substantial economic significance in the livestock industry around the world and it is an opportunistic human pathogen (De Alwis, 1993; Abdullah et al., 2013b). Haemorrhagic Septicaemia (HS) is an acute high mortality systemic disease of cattle and water buffaloes (De Alwis, 1992; OIE, 2012; Jesse et al., 2013c) leading to huge economic loss in the bovine industry particularly in South East Asia (De Alwis et al., 1990; OIE, 2008; Jesse et al., 2013a). However, in the context of susceptibility the buffaloes were found to be more susceptible to the disease in comparison to others (Rodostits et al., 2000; Ashraf et al., 2011; Jesse et al., 2013b). The common HS serotypes which have been reported to be responsible of recurrent outbreaks in Asia are the serotypes B: 2 (De Alwis, 1993; De Alwis et al., 1995; Khaleel et al., 2013; Abdullah et al., 2013b; Jesse et al., 2013a). In Malaysia, the stressful condition was during the raining season where most outbreaks occurred (Saharee, 1992; Abdullah et al., 2013b; Jesse et al., 2013a; Khaleel et al., 2013). The development of the disease in animals has been frequently reported to occur following exposure of the susceptible hosts to infections usually by the inhalation or ingestion of the bacterium (Saharee and Salim, 1991; Saharee, 1992; Shafarin et al., 2009; Ataei et al., 2009; Khaleel et al., 2013). The disease is characterized by a rapid course in the body temperature, respiratory rate, loud and stertorous breathing, profuse salivation, severe depression, anorexia and finally death which happens within 24 hours (Saharee, 1992; Rodostits et al., 2000; Khin et al., 2010 Jesse et al., 2013b; Jesse et al., 2013c).

Lipopolysaccharide (LPS) is the primary antigen for the identification of strains located in the outer membrane proteins (OMPs) of *Pasteurella multocida* type B: 2 and it is an important virulence factor by having a dominant role during the host immune-histopathological responses (Harper et al. 2011). In pathogens, LPS plays an imperative role in the disease process by interacting directly with innate host immune defences leading to the activation of a range of host immune cells, which can result in immuno-histopathological changes in the vital organs and blood tissue of death hosts (Raetz and Whitfield, 2002). Inoculated different doses of *Pasteurella multocida* type B: 2 and its LPS orally in mice or other experimental animals led to different degree of severity in tissue damage and inflammation in the host (Horadagoda et al., 2001; Jesse, 2011; Jesse et al., 2013a; Khaleel et al., 2013; Faez et al., 2013c).

Many researchers have elaborated on different routes and concentrations of *Pasteurella multocida* and its LPS to induced HS infection in experimental animals and their associated clinical signs (Boyce and Adler 2000; Abdullah et al., 2013a; Affandi et al., 2012; Jamal et al., 2013; Faez et al., 2013b). BALB/c mice challenged with as few as 20 cfu of *Pasteurella multocida* produce an overwhelming septicaemia within 30 hours of post-inoculation (Boyce and Adler 2000). In the present study, graded doses of *Pasteurella multocida* and its LPS was inoculated through the oral route and changes in clinical signs were observed 120 hours post inoculation.

The pathological modifications for HS are generalized lymphadenopathy, acute fibrinous pneumonia, proctitis, acute colitis, hemorrhagic typhilitis, submandibular and brisket edema (Benkirane and de Alwis, 2002; Abubakar and Zamri-Saad, 2011; Faez et al., 2013a). Jesse,

(2011) he was found in mice and calves after inoculated with *Pasteurella multocida* type B: 2 and its LPS showed variable clinical signs and histopathological changes including inflammatory cells, congestion, odema, degeneration and necrosis.

Hematological modifications caused by bacterial infections were detected during routine blood count. However, an animal's defensive mechanism can react quite differently to different bacteria; therefore, there was no singular pattern in complete blood count that indicated bacterial infection. Nevertheless, there are few abnormalities that are suggestive of bacterial infection such as neutrophilia with a left shift being the hallmark of acute inflammation (Walton, 2013; Guess et al., 2013). Recently, Jesse, (2011) and Abdullah et al., (2013c) found there were changes in the haematological parameters of Balb c mice inoculated with *Pasteurella multocida* type B: 2 and its LPS.

Cytokines are a diverse group of small proteins (<200 amino acids) that are secreted by a wide range of cell types for the purpose of intercellular signalling and communication. Interleukins (IL-1β and IL-6) are among some of the recognized cytokines (Dominique et al., 2006). The functions of IL-1β and IL-6 is to control the cell proliferation and differentiation, regulate the angiogenesis and immune responses (Clark, 2007). IL-1β is a potent pro-inflammatory cytokine produced by a variety of cell types such as monocytes, macrophages and neutrophils and endothelium (Monisha et al., 2012; Rania et al., 2014). IL-6 is a multifunctional cytokine and produced by a variety of cell types in both tissues of immune and endocrine systems (Kojima et al., 2002; Dominique et al., 2006; Tellervo et al., 2007).

Studies in Veterinary Medicine have demonstrated that the quantification of acute phase protein (APP) provides valuable clinical information in the diagnosis, prognosis and treatment monitoring of different pathologic processes (Martinez-Subiela et al., 2001; Eckersall and Bell, 2010; Tothova et al., 2013). Serum amyloid A (SAA) and Haptoglobin (Hp) increases during the acute-phase reaction within 24 hours and are involved in host defence (Eckersall and Bell, 2010; Tothova et al., 2013; Khaleel et al., 2013; Jesse et al., 2013b; Jesse et al., 2013c). The secreation of SAA and Hp depend on the different degree of severity in tissue damage and inflammation (Horadagoda et al., 2001; Jesse et al., 2013b; Jesse et al., 2013c; Khaleel et al., 2013; Faez et al., 2013a). Several research work had been carried out to determine the concentration of SAA and Hp in the serum of Balb c mice inoculated with *Pasteurella multocida* type B: 2 and its LPS (Jesse, 2011; Khaleel et al., 2013).

Nevertheless, knowledge of host cell responses towards the whole cell of *P. multocida* type B: 2 and its Lipopolysaccharide (LPS) with graded doses are still deficient in the natural host (cattle and water buffalo) and animal models such as mouse. There is no documentation on haematological, histopathological, interleukin-1β, interleukin-6, serum Amyloid A and Haptoglobin in Balb c mice inoculated orally with graded doses of *Pasteurella multocida* type B: 2 and its LPS.

Therefore, the objectives of present study are as follows:

1. To determine the clinical signs in mice following oral inoculation with graded doses of *Pasteurella multocida* type B: 2 and its lipopolysaccharide.

2. To determine the hematological and histopathological changes in mice following oral inoculation with graded doses of Pasteurella multocida type B: 2 and its lipopolysaccharide.

3. To determine the concentrations of interleukin-1β and interleukin-6 in mice following oral inoculation with graded doses of Pasteurella multocida type B: 2 and its lipopolysaccharide.

4. To determine concentrations of Serum Amyloid A and Haptoglobin in mice following oral inoculation with graded doses of Pasteurella multocida type B: 2 and its lipopolysaccharide.

Therefore the hypotheses of study are outlined below:

1. Oral inoculation of graded doses of *Pasteurella multocida* type B: 2 and its LPS in mice leads to modifications in the histopathological and hematological parameters.

2. Oral inoculation of graded doses of *Pasteurella multocida* type B: 2 and its LPS in mice leads to modifications in concentration of interleukin-1β and interleukin-6

3. Oral inoculation of graded doses of *Pasteurella multocida* type B: 2 and its LPS in mice leads to modifications in concentration of serum Amyloid A and Haptoglobin.

4. Oral inoculation of graded doses of *Pasteurella multocida* type B: 2 and its LPS in mice leads to modifications in clinical signs.

Therefore, the present study will provide additional information to fill the gap in HS study related to host cell responses due to graded doses of infections with *Pasteurella multocida* type B: 2 and its LPS following oral inoculation.

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