THE NEUROIMMUNOPHARMACOLOGY
OF ALCOHOL

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Discipline of Pharmacology

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August, 2011

A thesis submitted for the degree of Doctor of Philosophy
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Abstract

Background and purpose

Alcohol exposure induces glial toll-like receptor 4 (TLR4) signalling, while morphine administration leads to both TLR2 and TLR4 signalling in the central nervous system. However, the acute behavioural consequences of such immune activation remain unknown. This thesis aimed to examine: (a) the role of microglia, TLR2, TLR4, MyD88, and IL-1 receptor signalling in sedation and motor impairment following acute alcohol administration in mice; (b) the relationship between these observed behavioural effects and the changes in central and peripheral alcohol pharmacokinetic profiles; (c) the effect of alcohol on MAPK (ERK, JNK, and p38) and NFκB (IkBα) pathways and the alteration of such effects by attenuating microglial, TLR4, MyD88, and IL-1 receptor signalling ex vivo and in vitro; (d) the role of TLR2, TLR4, MyD88, IL-1 receptor, and µ opioid receptor (MOR) in the interaction between alcohol and morphine as assessed by sedation in mice; and (e) the association between the TLR4 Asp299Gly SNP and opioid or alcohol dependence in humans.

Experimental approach

In mouse studies and mouse cellular studies, pharmacological blockade of microglial signalling, TLR4, IL-1 receptor, or both MOR and TLR4 by minocycline, (+)-naloxone (the MOR-inactive isomer), IL-1 receptor antagonist, or (-)-naloxone (the MOR-active isomer), respectively, was utilised. Mice deficient in TLR2, TLR4, both TLR2 and TLR4, or MyD88 were used. The sedative effect of alcohol and the interaction between alcohol and morphine were assessed by the sleep time (loss of righting reflex) test, and alcohol dose-induced motor impairment was
determined by the rotarod test. The activation of MAPK cascade was determined by ERK, JNK, and p38 phosphorylation using a cytometric bead array assay, and the alteration in NFκB cascades was characterised via cellular IκBα protein levels utilising western blotting experiments.

In the human pharmacogenetic study, TLR4 Asp299Gly SNP genotypes were determined by a polymerase chain reaction (PCR)-restriction fragment length polymerase (RFLP) assay in 99 opioid dependent subjects, 100 alcohol dependent subjects, and 56 non-dependent healthy controls.

**Key results**

Pharmacological or genetic inhibition of microglial activation, TLR2, TLR4, both TLR2 and TLR4, MyD88, or IL-1 receptor signalling attenuated alcohol dose-induced sedation and motor impairment in mice. The modification of IκBα protein levels by alcohol exposure in vitro was time-dependent, and the increase in such protein levels was attenuated by inhibiting proinflammatory microglial activation, TLR4, MyD88, or IL-1 receptor signalling. In contrast, blocking the activities of TLR2, both TLR2 and TLR4, and MyD88, but not TLR4 or IL-1 receptor, inhibited the enhancement of alcohol’s sedative effect by morphine. The human genetic data showed a lack of association between alcohol or opioid dependence and TLR4 Asp299Gly polymorphisms.

**Conclusions and implications**

Collectively, these data suggest that in mice, alcohol activates microglial and TLR2- and TLR4-MyD88-NFκB-IL-1 receptor signalling rapidly, and this activation subsequently contributes to sedation and motor impairment induced by alcohol administration. However, TLR2-MyD88, but
not TLR4 and IL-1 receptor, cascade is involved in the interaction between alcohol and morphine. Such behavioural preclinical data provide novel insights into the immune mechanisms of the effects of alcohol and opioids.
Declaration

I, Yue Wu certify that this work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968.

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Yue Wu

Date
Acknowledgements

I would like to express my sincere gratitude to my supervisors, Prof. Andrew Somogyi, Dr. Janet Coller, and Dr. Mark Hutchinson, for leading me into medical research areas. Their extensive knowledge and logical way of thinking have been of great value to me. Their understanding and encouragement have provided a great basis for the present thesis.

The research presented in this thesis would have been impossible without the financial support from a China Scholarship Council (CSC)-University of Adelaide Joint Postgraduate Scholarship and a National Health and Medical Research Council (NHMRC) of Australia Grant-funded Supplementary Scholarship. I would also like to acknowledge the funding from a NHMRC project grant, an Australian Research Council (ARC) project grant, the Faculty of Health Sciences University of Adelaide, and the National Institute of Health (NIH, the United States of America) Intramural Research Programs of National Institute on Drug Abuse (NIDA) and National Institute on Alcohol Abuse and Alcoholism (NIAAA). I sincerely thank the various authorities for their travel grants to me, including NIDA-sponsored travel award in 2010, Postgraduate Travelling Fellowships for Health Science Research funded by University of Adelaide in 2010, and the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) student travel awards in 2009 and 2010, which supported me to attend and present my results at national and international conferences.

In particular, I acknowledge the help from the following people: Ms. Erin Lousberg and Dr. John Hayball for their assistance in western blotting; Dr. Lachlan Moldenhauer and Prof. Sarah Robertson for their help in flow cytometry; Dr. Simon Phipps and Prof. Paul Foster for kindly providing the genetic deficient mice; Dr. Kenner Rice for providing (+)-naloxone; Prof. Linda
Watkins for her support of this project; Dr. Daniel Barratt, Dr. Peter Athanasos, Dr. Andrea Gordon, Dr. Justin Hay, Dr. Sophie La Vincente, Dr. Erin Morton, Mr. Mario Nguyen, Mr. Aaron Farquharson, Ms. Eloise Gelston, and Mr. Dan Magan for conducting the original clinical studies from which my pharmacogenetic study drew its participants, and all the staff and students in the Discipline of Pharmacology, University of Adelaide.

I owe my most heartfelt gratitude to Ms. Sandy McConachy and Ms. Iris Liu for their care and encouragement since I arrived in Australia. I’m also very grateful to Ms. Jocelyn Ho and Ms. Erin Lousberg who helped me improve my written English. Thanks to my general practitioners and specialists, especially Prof. Justin Beilby, who helped restore my health.

To my colleagues in N529a, thanks for making it such a warm and cozy office. To all my housemates in Adelaide, thank you for being my brothers and sisters in Australia.

To my parents, other family members, and my friends in Beijing, thanks for your support and encouragement in the past three years. I especially want to thank A.Prof. Xianglin Zhang and those friends who helped me take care of my mother while I was not there.
Statement of Authorship

Attenuation of microglial and IL-1 signaling protects mice from acute alcohol-induced sedation and/or motor impairment


Impact Factor: 5.061

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Signed  Date  20/07/2011

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Provided critical evaluation of article

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Signed                   Date        01/08/2011

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Contributed to the experimental design, supervised the data interpretation and preparation of the manuscript, and acted as corresponding author

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Inhibiting the TLR4-MyD88 signalling cascade by genetic or pharmacologic strategies reduces acute alcohol dose-induced sedation and motor impairment in mice

Br J Pharmacol (2011): accepted paper

Impact Factor: 4.925

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Signed Date

Watkins LR

Provided critical evaluation of article

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Date  01/08/2011

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Date  29/07/2011
TLR2 and MyD88 mediate the sedative effect of alcohol and interaction between alcohol and morphine in mice


Impact Factor: 4.925

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Date  29/07/2011

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Signed  

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Signed Date 18/07/2011

Hayball JD

Provided null mutant mice and helped in manuscript evaluation

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Signed Date 18/07/2011

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Helped in manuscript evaluation

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Signed

Date 29/07/2011
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADH</td>
<td>alcohol dehydrogenase</td>
</tr>
<tr>
<td>ALDH</td>
<td>aldehyde dehydrogenase</td>
</tr>
<tr>
<td>ATP</td>
<td>adenosine triphosphate</td>
</tr>
<tr>
<td>B2M</td>
<td>β-2-microglobulin</td>
</tr>
<tr>
<td>BBB</td>
<td>blood-brain barrier</td>
</tr>
<tr>
<td>cAMP</td>
<td>cyclic adenosine monophosphate</td>
</tr>
<tr>
<td>CCL</td>
<td>chemokine (C-C) motif ligand</td>
</tr>
<tr>
<td>CCR</td>
<td>chemokine (C-C) motif ligand receptor</td>
</tr>
<tr>
<td>CD</td>
<td>cluster of differentiation</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>COX</td>
<td>cyclooxygenase</td>
</tr>
<tr>
<td>CTSF</td>
<td>cathepsin F</td>
</tr>
<tr>
<td>CTSS</td>
<td>cathepsin S</td>
</tr>
<tr>
<td>CXCL</td>
<td>chemokine (C-X-C) motif ligand</td>
</tr>
<tr>
<td>CYP</td>
<td>cytochrome P450</td>
</tr>
<tr>
<td>DA</td>
<td>dopamine</td>
</tr>
<tr>
<td>ERK</td>
<td>extracellular regulated kinase</td>
</tr>
<tr>
<td>GABA</td>
<td>gamma-aminobutyric acid</td>
</tr>
<tr>
<td>GFAP</td>
<td>glial fibrillary acidic protein</td>
</tr>
<tr>
<td>HBV</td>
<td>hepatitis B virus</td>
</tr>
<tr>
<td>IFN</td>
<td>interferon</td>
</tr>
<tr>
<td>IL</td>
<td>interleukin</td>
</tr>
<tr>
<td>IL-1RI</td>
<td>interleukin-1β receptor type I</td>
</tr>
<tr>
<td>IL-1ra</td>
<td>IL-1 receptor antagonist</td>
</tr>
<tr>
<td>iNOS</td>
<td>inducible nitric oxide synthase</td>
</tr>
<tr>
<td>Acronym</td>
<td>Full Form</td>
</tr>
<tr>
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<tr>
<td>IRAK4</td>
<td>interleukin-1 receptor-associated kinase 4</td>
</tr>
<tr>
<td>IRF3</td>
<td>IFN regulatory factor 3</td>
</tr>
<tr>
<td>IκBα</td>
<td>NFκB inhibitor α</td>
</tr>
<tr>
<td>JNK</td>
<td>c-Jun N-terminal kinase</td>
</tr>
<tr>
<td>LBP</td>
<td>LPS binding protein</td>
</tr>
<tr>
<td>LORR</td>
<td>loss of righting reflex</td>
</tr>
<tr>
<td>LPS</td>
<td>lipopolysaccharide</td>
</tr>
<tr>
<td>MAL</td>
<td>myelin and lymphocyte protein</td>
</tr>
<tr>
<td>MAPK</td>
<td>mitogen-activated protein kinase</td>
</tr>
<tr>
<td>MD-2</td>
<td>myeloid differentiation factor 2</td>
</tr>
<tr>
<td>MHC</td>
<td>major histocompatibility complex</td>
</tr>
<tr>
<td>MOR</td>
<td>μ opioid receptor</td>
</tr>
<tr>
<td>mRNA</td>
<td>messenger ribonucleic acid</td>
</tr>
<tr>
<td>MyD88</td>
<td>myeloid differentiation primary response gene 88</td>
</tr>
<tr>
<td>NAc</td>
<td>nucleus accumbens</td>
</tr>
<tr>
<td>NAD</td>
<td>nicotinamide adenine dinucleotide</td>
</tr>
<tr>
<td>NFκB</td>
<td>nuclear factor kappa-light-chain-enhancer of activated B cells</td>
</tr>
<tr>
<td>NMDA</td>
<td>N-methyl-D-aspartate</td>
</tr>
<tr>
<td>NO</td>
<td>nitric oxide</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
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<tr>
<td>PI3K</td>
<td>phosphoinositide 3 kinase</td>
</tr>
<tr>
<td>PKA</td>
<td>protein kinase A</td>
</tr>
<tr>
<td>PKC</td>
<td>protein kinase C</td>
</tr>
<tr>
<td>SN</td>
<td>substantia nigra</td>
</tr>
<tr>
<td>SNP</td>
<td>single nucleotide polymorphism</td>
</tr>
<tr>
<td>TIR</td>
<td>toll/IL-1 receptor</td>
</tr>
<tr>
<td>TLR</td>
<td>toll-like receptor</td>
</tr>
<tr>
<td>TNF-α</td>
<td>tumor necrosis factor-α</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
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<tr>
<td>TRAM</td>
<td>TRIF-related adaptor molecule</td>
</tr>
<tr>
<td>TRIF</td>
<td>toll/IL-1R domain containing adaptor inducing interferon-β</td>
</tr>
<tr>
<td>VTA</td>
<td>ventral tegmental area</td>
</tr>
</tbody>
</table>
**Human gene symbols**

<table>
<thead>
<tr>
<th>Gene symbol</th>
<th>Gene name</th>
<th>Protein</th>
</tr>
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<tbody>
<tr>
<td><em>ABCB1</em></td>
<td>ATP-binding cassette, sub-family B, member 1</td>
<td>P-glycoprotein</td>
</tr>
<tr>
<td><em>ADH1B</em></td>
<td>alcohol dehydrogenase 1B (class I), beta polypeptide</td>
<td>ADH1B</td>
</tr>
<tr>
<td><em>ADH4</em></td>
<td>alcohol dehydrogenase 4 (class II), pi polypeptide</td>
<td>ADH4</td>
</tr>
<tr>
<td><em>ALDH1A1</em></td>
<td>aldehyde dehydrogenase 1 family, member A1</td>
<td>ALDH1A1</td>
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<tr>
<td><em>ALDH2</em></td>
<td>aldehyde dehydrogenase 2 family (mitochondrial)</td>
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<td><em>CYP2B6</em></td>
<td>cytochrome P450, family 2, subfamily B, polypeptide 6</td>
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<td><em>CYP2E1</em></td>
<td>cytochrome P450, family 2, subfamily E, polypeptide 1</td>
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<td><em>CYP3A4</em></td>
<td>cytochrome P450, family 3, subfamily A, polypeptide 4</td>
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<td><em>GABRA6</em></td>
<td>gamma-aminobutyric acid (GABA) A receptor, alpha 6</td>
<td>GABA(_\alpha6)</td>
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<td>interleukin 10</td>
<td>IL-10</td>
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<td><em>IL1B</em></td>
<td>interleukin 1, beta</td>
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<td>interleukin 1 receptor antagonist</td>
<td>IL-1ra</td>
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<td>lymphocyte antigen 96</td>
<td>MD-2</td>
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<td><em>NFKB1</em></td>
<td>nuclear factor of kappa light polypeptide gene enhancer in B-cells 1</td>
<td>NFkB</td>
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<tr>
<td><em>OPRM1</em></td>
<td>opioid receptor, mu 1</td>
<td>MOR</td>
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<td>toll-like receptor 2</td>
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