Original Article

Innate Immunity

Innate Immunity
2016, Vol. 22(1) 51–62

DOI: 10.1177/1753425915615195
ini.sagepub.com

SAGE

Oral antibiotics increase blood neutrophil maturation and reduce bacteremia and necrotizing enterocolitis in the immediate postnatal period of preterm pigs

Duc Ninh Nguyen[1,*], Eva Fuglsang[2,*], Pingping Jiang[1], Malene M Birck[1], Xiaoyu Pan[1], Shamrulazhar BS Kamal[3], Susanne E Pors[2], Pernille L Gammelgaard[1], Dennis S Nielsen[3], Thomas Thymann[1], Ofer Levy[4], Hanne Frøkiær[2] and Per T Sangild[1,5]

Abstract

Immature immunity may predispose preterm neonates to infections and necrotizing enterocolitis (NEC). Intravenous antibiotics are frequently given to prevent and treat sepsis, while oral antibiotics are seldom used. We hypothesized that oral antibiotics promote maturation of systemic immunity and delay gut bacterial colonization and thereby protect preterm neonates against both NEC and bacteremia in the immediate postnatal period. Preterm pigs were given formula and administered saline (CON) or broad-spectrum antibiotics orally (ORA) or systemically (SYS) for 5 d after birth. Temporal changes in blood parameters and bacterial composition in the intestine, blood and immune organs were analyzed. Newborn preterm pigs had few blood neutrophils and a high frequency of progenitor cells. Neutrophils gradually matured after preterm birth with increasing CD14 and decreasing CD172a expressions. Preterm neutrophil and monocyte TLR2 expression and TLR2-mediated blood cytokine responses were low relative to adults. ORA pigs showed enhanced blood neutrophil maturation with reduced cell size and CD172a expression. Only ORA pigs, but not SYS pigs, were protected from a high density of gut Gram-positive bacteria, high gut permeability, Gram-positive bacteremia and NEC. Neonatal oral antibiotics may benefit mucosal and systemic immunity via delayed gut colonization and enhanced blood neutrophil maturation just after preterm birth.

Keywords

Antibiotics, neonatal immunity, neutrophils, preterm pig, TLR2

Date received: 20 August 2015; revised: 29 September 2015; accepted: 9 October 2015

Introduction

Neonatal immunity depends, to a large degree, on innate cells and soluble mediators for protection against environmental antigens and pathogens.[1,2] At birth, the innate immune system is immature,[3] and blood neutrophils and monocytes develop during late gestation and after birth, reflected by their increased expression of the surface receptors CD14, MD2, TLR2, and TLR4.[1,4–6] In pigs, these markers have similar trends during cell maturation,[1,4,5] whereas CD172a expression decreases postnatally.[7] Neutrophils also

[1]Section of Comparative Pediatrics and Nutrition, Department of Veterinary Clinical and Animal Sciences, University of Copenhagen, Frederiksberg, Denmark
[2]Department of Veterinary Disease Biology, University of Copenhagen, Frederiksberg, Denmark
[3]Department of Food Science, University of Copenhagen, Frederiksberg, Denmark
[4]Division of Infectious Diseases, Department of Medicine, Boston Children's Hospital and Harvard Medical School, Harvard, MA, USA
[5]Department of Pediatrics and Adolescent Medicine, Rigshospitalet, Copenhagen, Denmark

*DNN and EF contributed equally to this work.

Corresponding author:
Per T Sangild, Section of Comparative Pediatrics and Nutrition, Department of Veterinary Clinical and Animal Sciences, University of Copenhagen, Dyrlægevej 68, DK-1870 Frederiksberg C, Denmark.
Email: pts@sund.ku.dk