

Interleukin-1 receptor antagonist attenuates neuroinflammation in respiratory centers following lipopolysaccharide exposure in preterm fetal sheep.

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Background: Interleukin (IL)-1 β is upregulated during perinatal infection/inflammation and induces inflammation and injury in respiratory centres of the central nervous system (CNS) and breathing inhibition. We hypothesised that modulating interleukin (IL)-1 β , using an IL-1 receptor antagonist (IL-1Ra), would attenuate lipopolysaccharide (LPS)-induced neuropathology in CNS respiratory centres of preterm fetal sheep. **Method:** Chronically instrumented preterm fetal sheep (102 $\pm$ 1 days gestation (d)) were randomly allocated to receive intravenous (i.v.) saline infusions (n=7), repeated, escalating LPS infusions (0h=100ng, 24h=200ng, 48h=400ng; n=6; i.v.) or repeated i.v. LPS plus i.v. IL-1Ra infusions (10mg/kg) 24h after each LPS infusion (n=7). Post-mortem was performed after 12 days (114 $\pm$ 1d), and CNS respiratory centres were isolated for histopathological assessment. **Results:** LPS-exposure induced higher numbers of total and activated (STAT3+) microglia and astrocytes across forebrain and brainstem respiratory centres (P<0.05, vs control). LPS induced NeuN+ cell loss in the hypothalamus (P=0.01), pre-bötzing complex (preBötC) and nucleus tractus solitarius (NTS) (P=0.01 vs control). IL-1Ra treatment reduced total and activated microglia in the peri-aqueductal grey (PAG), preBötC, nucleus ambiguus and raphe nucleus (P=0.01 (all) vs LPS); and total and activated astrocytes across forebrain respiratory centres (P<0.01), preBötC, and hypoglossal nucleus (P<0.05 (all) vs LPS). The number of NeuN+ cells were increased with IL-1Ra in the hypothalamus, NTS and RN (P=0.01 vs LPS). **Conclusions:** IL-1Ra reduced LPS-induced neuropathology in CNS respiratory centres. Further studies are needed to determine if the histological attenuation of inflammation and injury in CNS respiratory centres with IL-1Ra will improve breathing function in preterm infants exposed to perinatal inflammation.