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Identification of kynurenine pathway enzyme mRNAs and metabolites in human placenta: Up-regulation by inflammatory stimuli and with clinical infection

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KEY WORDS
Intrauterine infection
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Quinolinic acid

Objective: The purpose of this study was to determine whether placental-derived kynurenines (neuroactive metabolites that are derived from tryptophan) contributes to infection-mediated fetal cerebral injury.

Study design: Placentae and cord blood were obtained from term deliveries (n = 16) and preterm deliveries with or without intrauterine bacterial infection (n = 8 per group). We investigated whether the placenta expressed messenger RNAs of kynurenine metabolite-forming enzymes, the effects of infection in vivo on the expression of these enzymes by the placenta, the in vitro effects of bacterial endotoxin lipopolysaccharide on expression and kynurenine metabolite output by the placenta, and the kynurenine metabolite levels in umbilical cord blood.

Results: Placentae expressed messenger RNA of tryptophan-degrading enzymes and synthesized several compounds. The expression of several enzymes increased significantly in placentae that were exposed to infection and/or lipopolysaccharide. Lipopolysaccharide also induced significant increases in placental kynurenine and quinolinic acid output. Kynurenine and quinolinic acid in cord blood of fetuses who were exposed to infection were elevated significantly.

Conclusion: Inflammatory mediated release of kynurenines from placentae exposes the fetus to significant amounts of potentially neurotoxic substances.

Intrauterine infection is recognized as a major risk factor for preterm premature rupture of membranes (PPROM), preterm birth,[1] and neurologic impairment in the newborn infant.[2] Vasculitis of the umbilical cord and clinical and histologic chorioamnionitis are recognized as major risk factors of intraventricular hemorrhage and cystic periventricular leukomalacia and the subsequent development of cerebral palsy in early postnatal life.[3,4] Studies that involve pregnant rodents confirm that

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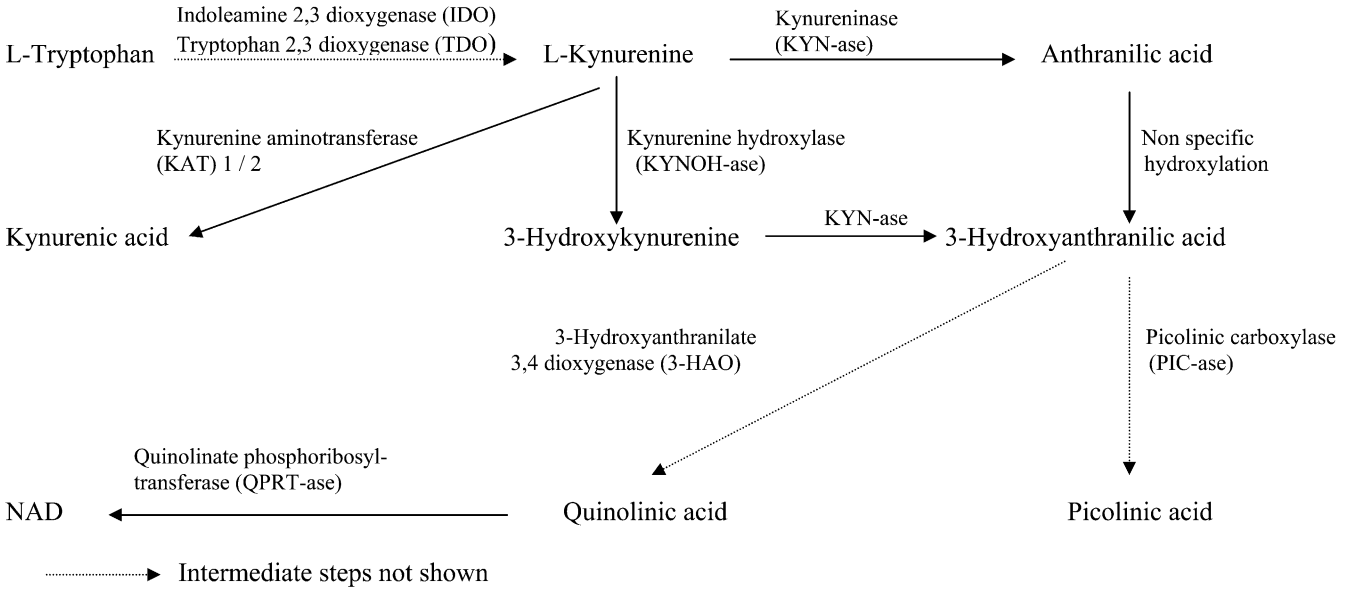

Metabolite	Neuroactivity
Kynurenine	Neuronal apoptosis
Kynurenic acid	NMDA receptor blockade, anti-convulsant, neuroprotectant
3-Hydroxyanthranilic acid	Neurotoxin, free radical mediated damage, potentiates quinolinic acid toxicity
Picolinic acid	Oxygen free radical mediated damage
Quinolinic acid	Activates NMDA receptors, excitotoxin, convulsant, free radical mediated damage

Figure 1 The kynurenine pathway of tryptophan catabolism. Several intermediate metabolites that formed are shown; the *arrows* indicate the enzymes that were involved in their synthesis. Neuroactive properties of some of these substances are also listed.

the fetal inflammatory response plays a major role in the genesis of this damage.[5] However, despite increased levels of proinflammatory cytokines in fetal plasma and amniotic fluid,[6,7] it is uncertain whether the fetal inflammatory response alone can cause such damage in the human.[8]

An alternative hypothesis is that critical enzyme systems within the placenta may respond to inflammation of maternal systemic, ascending vaginal, or intrauterine origin and release substances that are capable of damaging the developing fetal brain. Indoleamine 2,3-dioxygenase (IDO) is a monomeric heme-containing enzyme that is present in abundant levels in the human placenta.[9] IDO catalyzes the rate-limiting step in the breakdown of the essential amino acid L-tryptophan to kynurenine that provides a substrate that can be degraded further into a number of metabolites with neuroactive properties. Figure 1 shows the metabolites formed and enzymes involved in tryptophan catabolism to nicotinamide adenine dinucleotide by way of the kynurenine pathway and neuroactive properties of some of these substances. Although these kynurenines are produced in the adult brain, liver, and monocytes, it is unknown whether the placenta is able to convert kynurenine into any of the downstream metabolites.

Studies have also shown that proinflammatory cytokines induce the expression of several enzymes that are involved in tryptophan catabolism.[10] In the adult rodent brain, inflammatory-mediated enzyme expression results in the high output of metabolites such as 3-hydroxykynurenine and quinolinic acid (QUIN) and produces changes in white matter[11] that are characteristic of cystic periventricular leukomalacia. Thus, it is possible that the inflammatory induction of kynurenine synthesis and further conversion in the placenta to neuroactive products (Figure 1) could contribute to the pathogenesis of infection-mediated cerebral injury in the fetus. Therefore, the aims of this study were to determine whether the human placenta was capable of producing kynurenine metabolites, whether placental output of these substances was altered in the presence of intrauterine infection, and whether these substances were present in the umbilical circulation.

Material and methods

Subjects

Healthy pregnant women who were delivered at term (n = 16 women; mean gestational age, 39 weeks), subjects with PPROM with fever, maternal tachycardia, discharging foul smelling cloudy amniotic fluid, and subjects with PPROM but without these clinical signs of