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Immunohistochemical study of apoptosis and glial activation markers in the substantia nigra of the human neonate: The effect of perinatal hypoxic/ischemic injury

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Perinatal hypoxic/ischemic injury (PHI) remains a major cause of mortality and morbidity that can generate permanent neurological and/or mental deficits later in life. Our previous studies showed increased vulnerability of the dopaminergic neurons of the human substantia nigra (SN) to prolonged PHI (Pagida et al., 2013,72:337). In SN neurons, we observed a dramatic reduction of tyrosine hydroxylase (first and limiting enzyme in dopamine synthesis) and of their cellular size. In order to investigate if the above observations represent an early stage of SN degeneration, we studied immunohistochemically cleaved caspase-3 (CCP3, marker of apoptosis) and Apoptosis Inducing Factor (AIF, death marker), Iba-1 (marker of microglia activation) and GFAP (marker of astrocytes) in the SN of the human neonate in relation to the severity/duration of PHI, as estimated by neuropathological criteria. Our material included mesencephali of 22 autopsied neonates (corrected age ranging from 34 to 46.5 weeks of gestation) obtained after written parental consent. Our results showed rare CCP3-positive neurons and glia, while few neurons were found dying through an AIF-mediated pathway. Morphological variety of microglial phenotypes was revealed in the SN, indicating a variable degree of microglial activation, with a particular increase in cases with acute PHI. Extensive astrogliosis was observed not only in the SN, but also in the whole mesencephalon of neonates with acute PHI, while astrocytes were limited in the mesencephalic gray matter in neonates with prolonged PHI. Our study showed a widespread activation of microglia and astrocytes in the absence of extensive neuronal death in the SN of the human neonate. By contrast, experimental studies in rats and sheep had revealed inflammation (Ezquer et al.,2006,197:391) with an increased number of apoptotic neurons in the SN after PHI (Oo et al., 1995,69:893; Castillo-Melendez et al.,2004,55:864). The activation of microglia and astroglia observed in human neonates could therefore be neuroprotective for the mesencephalon supporting the viability of SN neurons after PHI. Our study provides additional insights into the protective role of microglia and astrocytes in the SN of the human neonate under PHI.

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Effects of phenformin on hypoxia-induced microglia activation

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