Is hypoxia-inducible factor 1 an actor in migraine pathogenesis? An experimental study of possible metabolic facets including hypoxia and mitochondrial impairment.

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Background. Reduced mitochondrial phosphorylation potential was shown in migraineurs between attacks. Hypoxia and NO can trigger migraine attacks by hitherto unknown mechanisms. Both hypoxia and NO donors up-regulate hypoxia-inducible factor 1 (HIF-1), which increases the transcription of genes coding for proteins that promote blood flow, inflammation and NO-synthase expression. We postulate that HIF-1 could be a pivotal link between impaired oxygen metabolism, NO and trigeminovascular activation and play a key role in migraine pathophysiology.

Objective. As a first step, we decided to determine if hypoxia, NO donors and CoCl2 (a chemical HIF-1 inducer) can activate trigeminovascular nociceptors in rat.

Methods. Male Sprague-Dawley rats were submitted to either hypoxia (8% O2, 1 hour), normoxia, nitroglycerin (10 mg/kg), CoCl2 (30 mg/kg) or saline injections (1 ml/kg). Immunohistochemical expression of c-fos was quantified as an indicator of neuronal activation in the superficial laminae of trigeminal nucleus caudalis and dorsal horns of thoracic spinal cord in animals sacrificed 4 or 5 hours post-treatment.

Results. In our study there was no significant increase of c-fos immunoreactive nuclei after hypoxia or NTG. By contrast, CoCl2 induced a significant enhancement of c-fos expression exclusively in trigeminal nucleus caudalis.

Conclusion. For unknown reasons, we were not able to reproduce the NTG effects reported by others (Tassorelli et Joseph, 1995). CoCl2, however, may be a novel experimental model to study metabolic activation of the trigeminovascular system. Whether its effect involves HIF-1 and/or is due to its ability to alter mitochondrial functions is being determined.