Epigenetic changes and neonatal procedural pain

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Abstract:

Worldwide, 11% of pregnancies result in premature birth and as a consequence the hospitalization of these neonates in the neonatal intensive care unit (NICU). During their stay in the NICU, neonates undergo a mean of 10-14 painful procedures a day, often without adequate analgesia. Furthermore, exposure to neonatal pain has long-term effects outlasting NICU hospitalization: for instance, infants hospitalized in the NICU have a higher need for analgesic during adult surgery and are more prone to develop post-operative pain. In order to manage the long-term effects of neonatal pain and to provide adequate acute pain treatment during the NICU stay, understanding of the underlying mechanism and the plasticity of the pain network is of utmost importance and thus pre-clinical research is required. Previous research using a translational animal model developed in collaboration with Sophia Children's Hospital in Rotterdam provided insights into the mechanism and plasticity of the pain network during the NICU stay: adult animals previously exposed to neonatal procedural pain develop decreased levels of u-opioid receptor in the spinal dorsal horn following later life injury. The

pharmacological modulation with use of methadone, a drug to modulate not only the u-opioid receptor but also of the NMDA-receptor, has been shown to inhibit the acute and long-term effects of neonatal pain. For both u-opioid and NMDA receptors, epigenetic mechanisms are known to be involved in the regulation of their expression following painful experiences. With this in mind, the present study aims at investigating if epigenetic changes mediates the long-term effects of neonatal procedural pain, using an animal model of neonatal procedural pain. Between day of birth and post-natal day 7, rat pups were subjected to four needle pricks a day. At 8 weeks of age, adult animals underwent surgery on their left hind paw and the development and maintenance of post-operative pain were assessed using von Frey filaments. Epigenetic changes as based on methylation status of genes coding for u-opioid- and of NMDA-receptor will be measured in the dorsal lumbar spinal cord before and after surgery in the adult rat.