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| Topics: **SIDS/SUID** |
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| **Substance P deficiency and respiratory arrest in SIDS - likely mechanisms** |
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| **Introduction** Sudden infant death syndrome (SIDS) involves failure of arousal to potentially life threatening events during sleep, including hypoxia. While neuronal dysfunction, and particular neurotransmitter control, has been implicated, the specific pathways associated with cardiorespiratory failure are unknown. The neuropeptide substance P (SP) functions within key medullary nuclei to regulate cardiorespiratory and autonomic function in conjunction with serotonin (5-HT). Actions of SP are primarily mediated by neurokinin 1 receptors (NK1R) in the CNS and SP is recognized as a primary excitatory neurotransmitter and central mediator of cardiovascular reflexes such as baroreceptor sensitivity and chemoreceptor reflex modulation in response to hypoxia. Therefore the SP/NK1R network has been previously implicated in the pathogenesis of SIDS with variable results. In the current study tissue receptor autoradiography was used to map the distribution and binding density profile of the NK1R to 14 specific nuclei intimately related to cardiorespiratory function in the human infant medulla of 55 SIDS and 44 control infants.  **Material and Methods** Infant brainstem specimens were accrued from the Office of the Chief Medical Examiner in San Diego and the study approved by the committee on clinical investigation at Boston Children’s Hospital. Tissue receptor autoradiography examined the medullae of 99 infants, from three separate datasets. Determination of SP receptor specific binding density was performed using 0.15nM 125I Bolton Hunter labeled Substance P autoradiography. Quantitative densitometry analysis of total and non-specific binding density was measured in fmol/mg in the specific nuclei of interest to allow comparison of binding density between SIDS and control infants. Total receptor binding was determined in two sections and non-specific receptor binding in one section for each nucleus analysed.  Specific receptor binding density was determined by subtracting nonspecific binding from total binding.  **Results** Statistical ANCOVA models controlling for postnatal age (PNA), prematurity status, sex and dataset of origin showed significant differences in binding levels between SIDS and controls. SIDS cases had significantly decreased NK1R binding density in six medullary nuclei including the nucleus tractus solitarius (NTS), all three subdivisions of the inferior portion of the olivo-cerebellar complex; the principal inferior olivary complex (PIO), medial accessory olive (MAO) and dorsal accessory olive (DAO), the gigantocellularis nucleus (GC) and the raphe obscurus (ROb).  **Conclusions** A significant reduction in NK1R binding density in six specific medullary nuclei may contribute to the defective interaction of critical medullary mechanisms with cerebellar sites, resulting in an inability to elicit appropriate motor and respiratory responses in SIDS. SP/NK1R dysfunction in conjunction with defects in multiple other neurotransmitter systems within the same nuclei may contribute to the primary failure in a subset of SIDS deaths.  **Funding source:** River’s Gift International SIDS Fellowship |
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