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Hyperplasia of the aorticopulmonary paraganglia in infants dying of SIDS: further supports for the cardiorespiratory hypothesis

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Introduction

Investigations into the pathogenesis of the sudden infant death syndrome (SIDS) have focused on abnormalities in the regulation of breathing during sleep. Various studies of infants, some of whom subsequently died of SIDS, have reported altered sleep patterns (1), abnormalities in respiratory and heart rate activity (2), episodes of prolonged apnea (3-6), and excessive periodic and short apnea (7,8). The mechanisms by which these risk factors could precipitate terminal apnea in susceptible infants remain to be understood (1-8).

Neural control of respiration involves the integration of three systems (9). The first is the motor system, which initiates and maintains respiration. The second is the mechanoreceptor system, which responds to stretch to regulate the rate and volume of respiration via the vagus and glossopharyngeal nerves. The third component is the chemoreceptor system, which includes central and peripheral chemoreceptors (PC), neural afferents and neurohormonal effectors which alter both pulmonary performance (rate and depth of breathing) and cardiovascular performance (ventricular performance and regional blood flows and perfusion pressures) (10-12).

Since intact PC are essential for respiratory control, especially to respond to hypoxia, these structures have been investigated in SIDS.

Peripheral chemoreceptors and SIDS

Over the last 20 years or so, the morphology of the carotid bodies (CB), located at the junction of the external and internal carotid arteries, has been the subject of several studies on SIDS. In general, however, the findings have been conflicting. Naeye *et al.* (13) found the glomic tissue to be present either in abnormally increased or in abnormally decreased amounts, the former more prominent in victims with more severe antecedent chronic hypoxia. Lack *et al.* (14) observed that CB combined weights were slightly heavier in SIDS cases, but the computerized planimetry of total surface area and the area occupied by "functional parenchyma" revealed no significant differences between SIDS and control groups. Furthermore, chief cells showed a similar intense degree of cytoplasmic argyrophilia in both groups (14) and ultrastructural studies were contradictory (14-16). Although, these data were not supportive of CB having a significant role in the pathogenesis of SIDS, further investigation on PC is warranted.

The specific function of the vagal body paraganglia (VBP), located at various points along the peripheral distribution of the vagus nerve, is still unclear (10). They are small groups of glomic tissue, typically situated in side the perineurium, just beneath the nerve sheath or between nerve fibers (10), which cannot be distinguished microscopically or cytochemically from the other PC (17). Hyperplasia of the VBP has been noted in patients with chronic hypoxemia, supporting a chemoreceptor function for this neuroendocrine tissue (18). In SIDS, no significant differences in microanatomy were reported compared with controls, however, an underlying functional abnormality with autonomic malregulation was not excluded (17).

Located within the epithelial lining of the pulmonary airways, the neuroepithelial bodies (NEB) are considered intrapulmonary chemoreceptors. Compensatory hyperplasia of the NEB has been described in the lungs of SIDS victims, characterized by an increase in the frequency, size and mean concentration of bombesin-like peptide of the neuroepithelial cells, when compared to values of age-matched controls (19,20). Furthermore, the frequency and size of pulmonary NEB immunostained for bombesin was increased twofold in two cases of congenital central hypoventilation syndrome (CCHS), a rare disorder of unknown etiology characterized by failure of the respiration control (21). Since NEB are thought to function as hypoxia-sensitive airway chemoreceptors, it has been speculated that chronic hypoxia and/or brainstem dysfunction may be responsible for this alteration, contributing to the pathophysiology of SIDS and related conditions such as CCHS (19-21).

Aorticopulmonary paraganglia as a peripheral chemoreceptor

Although there is glomus tissue in a variety of sites throughout the body, the most important are the CB and the aortic bodies, also known as aorticopulmonary paraganglia (APP), which are a more diffuse group of small glomera primarily situated in the aortic arch (10,11). Little is known about the pathology of the APP. Although they are a critical component of respiratory control, their neuroanatomic complexity has limited investigation in human disease (22-24). Histologically, they consist of small groups of lobules of glomic tissue separated by a well vascularized connective tissue with a prolific supply constituted by nerve bundles and ganglion cells (10,11). Each lobule contains several distinct cell clusters consisting of central cores of chief (glomus Type I) cells surrounding by thin rims of elongated sustentacular (glomus Type II) cells (10,11). Currently, most investigators favor the chief cells, containing dense-core neurosecretory

granules, as being the chemosensitive element or transducer within the APP with presumed chemoreceptor function (25).

Only a few investigators have paid attention to the possible role of the APP in pathological processes involving cardiorespiratory disturbances (22,26,27). In previous studies, we had described an increased glomic tissue of the APP in some cases of SIDS, suggesting that this alteration could have a role in the pathophysiology of the syndrome (24,28,29).

Aorticopulmonary paraganglia in infants dying of SIDS

Enlargement of the APP in some infants dying of SIDS has already been described previously (24,28), a finding which was confirmed with the use of more sophisticated morphometric techniques. This alteration, present in 24% of our SIDS cases, can be promptly inferred from sections under the low power objective of the microscope, nevertheless, an unequivocal proof of glomic cell proliferation can only be confirmed by morphometrical measurement. The normal appearance of a few, small, discrete lobules separate from the fibroadipose tissue was lost and individual lobules showed great enlargement with irregular and elongated profiles. The enlargement of the APP was due in small part to an increase in the number of lobules but, more importantly, to an increase in size of lobules. The cell clusters and cell diameters were not significantly different from age-matched controls, thus enlargement of the APP involved an increase in the number rather than size of cells, favoring hyperplasia more than hypertrophy.

Prominence of dark cells may be superimposed on the histological features of APP hyperplasia. These were distributed diffusely throughout the glomic tissue, exhibiting a compact basophilic cytoplasm, often in strap-like cytoplasmic extensions with an eccentric hyperchromatic nucleus. This aspect has been attributed to a greater concentration of biologically active peptides, such as leucine- and methionine-enkephalins (30). The high

number of cells containing endogenous peptides may have pathophysiological significance, since increased levels of enkephalins have been associated with a reduced ventilatory drive to hypoxia (30). Furthermore, it has been reported that, in hyperplastic conditions, the cores of dark cells can become spaced, leaving fewer chief cells per unit area as compared with the controls (30), which would explain the lightly smaller density of chief cells observed in our cases in spite of hyperplasia.

Previous reports described a more extensive and prominent distribution of paraganglion cells in human fetus and newborn infants than in adults (10,32). The mechanisms underlying this morphologic variation are not yet known (31). Programmed cell death may play a role in the process, since apoptosis has been well-established as a normal event in the course of fetal nervous system development (32). This normal "shaping or molding" with age was not observed in the SIDS group. The APP volumes in these cases appeared to be already increased in the younger group and remained practically the same in all age intervals, suggesting that the proliferate stimulus (hypoxia, trauma or irritation) could be produced or initiated during fetal development or in the early postnatal period. This stimulus could produce structural and/or functional alterations in the chemoreceptor cascade of the late-term fetus or newborn infant, preventing them from responding promptly to chemical stimuli. This hypothesis could explain why infants at increased risk from SIDS showed a deficient sleep arousal to hypoxia, especially in the first postnatal week, which did not vary over the first three months of postnatal life (33).

Final comments

Glomic tissue is often hyperplastic in animals and human beings who are chronically hypoxemic (13). The implications of these changes are poorly understood at present (33). The abnormality responsible could be primary in the organ or it could reside in brain stem respiratory centers and their efferent or afferent connections to the PC (13). In fact, the most recent focus of research on SIDS has been in the development of neuronal circuitry, involving brainstem neurons (34-36). In some SIDS victims, an underlying vulnerability can be a volume reduction of the arcuate nucleus (ARC) (37,38), which has been considered an essential chemoreceptive component of the neuroanatomic circuitry involved in cardiorespiratory modulation (38). In fact, ARC interactions with the PC have been investigated (39,40). The glomic tissue hyperplasia observed in some cases of SIDS could be compensatory, beginning from alterations in the central chemoreceptor mechanisms. Ongoing research in our laboratory is designed to document, histopathologically, eventual links between abnormalities of the central and peripheral chemoreceptor apparatus in SIDS victims.

Babies who die of SIDS may born with one or more vulnerabilities that probably result from adverse conditions or abnormalities in the early stages of fetal development (41). These vulnerabilities may prevent the infants from responding normally to internal and external influences that place special demands on their bodies. Some hypotheses of apnea have emphasized a failure in the generation of rhythmic breathing during sleep (42), while others have proposed an increased threshold to arousal from sleep during irregularities of breathing such as prolonged apnea or inflammation of the respiratory tract (43) These hypotheses suggest that a subtle developmental disorder produces respiratory instability in susceptible infants (42,43) When these high-risk infants are exposed to triggering factors

in the environment, the end result would be an episode of terminal apnea (44). The physiological mechanisms by which these risk factors could precipitate terminal apnea in susceptible infants remain to be understood (44) A defect in the APP chemoreception could have an important role in this respiratory instability.

Potential dysfunction of the APP system, considered the first line of defense against hypoxia (12,21), could play a role in the pathogenesis of SIDS. It has been reported that an altered chemosensitivity would lead to progressive hypercabia and a cascade of progressive CO_2 narcosis during sleep, diminished arousal, impaired airway defense reflexes, worsening hypoventilation, and eventual apnea and death (41). Subtle differences in symptoms could indicate that, since birth, the SIDS infants are different from controls, some having dysfunction of the airway controls. It is also possible that APP hyperplasia may not be restricted to SIDS deaths. Clearly, additional studies are needed to determine the role of these APP abnormalities in the pathophysiology of SIDS.

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