Serotonin, gasping, autoresuscitation, and SIDS—a contrarian view

J. C. Leiter
Department of Physiology, Dartmouth Medical School, Lebanon, New Hampshire

IN THEIR STUDY in the Journal of Applied Physiology, Erikson and Sposato (4) induced anoxic apnea in neonatal Pet-1 knockout (KO) and wild-type mice at postnatal day (P) 4.5 and P9 and examined the subsequent quality of gasping and autoresuscitation while the animals breathed room air. Pet-1 KO mice lack ~70% of the usual number of serotonergic neurons, and they have brain tissue serotonin (5-HT) levels that are ~15% of the normal value (6). Both the onset of gasping and the restoration of eupnea were delayed once anoxic apnea developed in the Pet-1 KO animals compared with wild-type animals. However, the actual number of gasps and quality of gasping was remarkable similar in wild-type and mutant animals. Finally, the prolonged latency in the onset of gasping and in the restoration of eupnea was less pronounced in Pet-1 KO animals on P9 compared with Pet-1 KO animals on P4.5 (the Pet-1 KO animals seemed to be “outgrowing” the abnormalities of autoresuscitation), although the older Pet-1 KO animals did not initiate gasping or restore eupnea as quickly as similarly aged wild-type animals. Three issues, the function of serotonin in autoresuscitation, the function of serotonin in gasping, and the relevance of these studies to sudden infant death syndrome (SIDS), deserve comment.

Studies of deficiencies of serotonin in neonatal animals, whether created pharmacologically or genetically, have not consistently created respiratory or cardiovascular control abnormalities that supported previous hypotheses about the pathogenesis of SIDS (8, 10). This has been a surprise and a disappointment. For this reason, investigators have turned their attention away from analyses of cardiorespiratory control (e.g., responses to hypoxia or hypercapnia) toward studies of integrated responses, such as autoresuscitation, that may limit apnea duration or restore eupnea after apnea occurs—the research emphasis has shifted from factors that may cause respiratory instability toward the factors that limit the damaging effects of respiratory instability. Autoresuscitation may be an essential element sustaining viability given the surprising high frequency of apneas even in normal neonates (19). Abnormalities in the process of initiating gasping or restoring eupnea (these are probably mechanistically separable processes) may contribute to the pathogenesis of SIDS (14, 16) since some risk factors for SIDS have adverse effects on autoresuscitation (5, 9, 15). In addition, it now appears that deficient serotonergic function impairs coordinated transitions between eupnea and gasping in neonatal animals (4, 17, 18).

Despite the abnormalities initiating gasping and restoring eupnea, the actual gasps were remarkably normal. Therefore, these data do not support the contention, derived from work in animals, that serotonin is absolutely required for gasping (20). Studies in more intact preparations, which are more relevant to studies of human neonates, indicate that gasping can occur in the complete absence of serotonin, or as close to the complete absence as one can get (4, 17, 18). This does not mean that serotonin is unimportant in autoresuscitation, but it does seem that serotonin affects the regulation of the transitions from eupnea to gasping and from gasping to eupnea rather than the gasping mechanism itself.

Panigrahy et al. (12) first found that serotonin receptor binding was diminished in babies who died of SIDS. This finding has been confirmed repeatedly, and it is the single most consistent abnormality in SIDS victims; it really cannot be ignored in any pathogenetic scheme of SIDS. There has been a tendency ever since this original description of reduced serotonergic receptor binding to model SIDS by reducing serotonergic activity (10). Therefore, the work by Erikson and Sposato (4) should be a cause for celebration; the results provide a plausible mechanism whereby serotonin deficiency may contribute to SIDS. Moreover, there have been four additional papers in the last year using genetically modified mice to interfere with some aspect of serotonergic function that also describe abnormalities that might plausibly be related to SIDS (1, 7, 11, 18). But don’t break out the champagne yet; I suspect that none of these animal models recreates the most important serotonergic abnormalities in SIDS—the level of serotonergic activity and the actual level of serotonin in the brain stem. In subsequent neuropathological analyses of SIDS victims, a more nuanced description of the serotonergic abnormalities has emerged. The number of medullary serotonergic neurons was actually increased; 5-HT1A receptor binding was decreased (the 5-HT1A receptor is often a presynaptic inhibitory autoreceptor on serotonergic neurons in the medulla); and the density of the serotonin transporter (5-HTT or SERT) per serotonergic neuron was reduced (13). Stated another way, babies who died of SIDS had increased serotonergic numbers, were less able to clear serotonin from the extracellular space, and, presumably, had reduced inhibition of serotonergic activity. Metabolites of serotonin were also elevated in the spinal fluid of babies who died of SIDS compared with a control group of infants (3), which is consistent with the hypothesis that serotonin activity and serotonin levels may be elevated in infants who died of SIDS, not diminished as we have assumed in virtually all of our previous experimental designs.

As shown in Table 1, genetically modified mice, which allegedly model some aspects of SIDS, have not accurately recreated the phenotypic characteristics of babies who died of SIDS. Pet-1 KO mice have reduced numbers of serotonergic neurons and reduced tissue levels of serotonin in the brain. Even though Pet-1 KO mice demonstrate abnormalities of autoresuscitation (4, 18), they do not mimic the neuropathological phenotype of babies who died of SIDS. The same criticism is true of mice with selective knockout of Lmx1b in Pet-1 expressing cells (Lmx1b+/−). These animals lack all serotonergic neurons, and the brain tissue serotonin levels are very low. Adult Lmx1b+/− KO mice have abnormalities of respiratory control and thermoregulation (7), and these results help define the minimum behavioral functions of serotonin, but...
they are not necessarily relevant to SIDS. Similarly, transgenic mice in which the 5-HT1A receptor was overexpressed (the exact opposite of the receptor phenotype in babies who died of SIDS) had reduced serotonergic neuronal activity after tryptophan administration and reduced levels of the serotonin metabolite, 5-hydroxyindole acetic acid, in the brain (1). Overexpression of the 5-HT1A receptor was associated with cardiovascular and thermal instability between ~P25 and P80, very late in murine development for a model of SIDS. Last, mice in which the serotonin reuptake transporter had been knocked out had, as adults, increased serotonin in the extracellular space, but the 5-HT1A receptors were reduced in number and desensitized, and serotonergic neuronal activity was reduced (2). Male mice studied as adults had reduced ventilatory sensitivity to CO2 (11). This last model is closer to a SIDS serotonergic phenotype, but my personal bias is that serotonergic activity is increased, not decreased, in babies who are vulnerable to SIDS. Thus genetic and pharmacological studies have modeled SIDS by creating deficiencies of serotonergic activity—yet if serotonergic levels and serotonergic activity are actually elevated in SIDS, we have been marching in the wrong direction, and none of the abnormalities described in these animals, interesting and informative though they may be, has anything to do with the function of serotonin in the pathogenesis of SIDS. The hypothesis that serotonergic activity is reduced in SIDS currently dominates research in the field, but perhaps it is time to entertain the opposite, but equally plausible, hypothesis that SIDS is actually caused by excess serotonergic activity.

REFERENCES


Table 1. Summary of serotonergic phenotypes in humans who died of SIDS and recent genetic models of SIDS

<table>
<thead>
<tr>
<th>No. of serotonergic neurons</th>
<th>Pet-1 KO Mice</th>
<th>Lmx1β KO Mice</th>
<th>Overexpression of 5-HT1A Receptor (Mice)</th>
<th>5-HT KO Mice</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT₁α receptor binding</td>
<td>↑↓</td>
<td>↓↓</td>
<td>↑↓</td>
<td>↑↓</td>
</tr>
<tr>
<td>5-HTT level</td>
<td>↑cell</td>
<td>↓</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tissue (T) or CSF (C) serotonin level</td>
<td>↑C</td>
<td>↓</td>
<td>↑T</td>
<td>↓</td>
</tr>
<tr>
<td>Serotonergic neuronal activity</td>
<td>↑ (? )</td>
<td>↓</td>
<td>↑T</td>
<td>↓</td>
</tr>
</tbody>
</table>

SIDS, sudden infant death syndrome; KO, knockout; CSF, cerebrospinal fluid; 5-HTT, serotonin transporter; ↑, increased; ↓, decreased; (?), not measured explicitly (in so far as I can tell), but this is the presumed direction of change; nl, normal; 0, absent.