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 apneas occur—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 surprisingly 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 some risk factors for SIDS have adverse effects on 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/p/p). These animals lack all serotonergic neurons, and the brain tissue serotonin levels are very low. Adult Lmx1b/p/p KO mice have abnormalities of respiratory control and thermoregulation (7), and these results help define the minimum behavioral functions of serotonin, but
Table 1. Summary of serotonergic phenotypes in humans who died of SIDS and recent genetic models of SIDS

<table>
<thead>
<tr>
<th>Human SIDS Victims</th>
<th>Pet-1 KO Mice</th>
<th>Lmx1βKO Mice</th>
<th>Overexpression of 5-HT1A Receptor (Mice)</th>
<th>5-HTT KO Mice</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of serotonergic neurons</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>5-HT1A receptor binding</td>
<td>↓</td>
<td>↑</td>
<td>0</td>
<td>nl(?)</td>
</tr>
<tr>
<td>5-HTT level</td>
<td>↓/cell</td>
<td>↓</td>
<td>0 or ↑(?)</td>
<td>nl(?)</td>
</tr>
<tr>
<td>Tissue (T) or CSF (C) serotonin level</td>
<td>↑/T</td>
<td>↓</td>
<td>↑T</td>
<td>↑T</td>
</tr>
<tr>
<td>Serotonergic neuronal activity</td>
<td>↑(?)</td>
<td>↓</td>
<td>↓</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.

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 babies who are vulnerable to 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