Preview

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Possible role of astrocytes in the sudden infant death syndrome (SIDS)

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SIDS is defined as the sudden unexpected death of an infant< 1 year of age, with onset of the fatal episode apparently occuring during sleep and which remains unexplained after a thorough investigation, including performance of a complete autopsy and review of the circumstances of death and the clinical history.

Recently, Duncan et al. (2010) reported that brainstem serotonin (5-HT) and tryptophan hydroxylase (TPH2) levels were lower in SIDS cases than in age-adjusted controls, providing further evidence that defects in the medullary serotonergic system are important in SIDS. This finding indicates that 5-HT levels were low as a result of decreased synthesis rather than increased degradation.

Despite the assumption that SIDS results from the simultaneous occurrence of an underlying vulnerability in the infant, a critical developmental period during infancy, and exposure of an infant to an exogenous stressor („triple-risk" hypothesis, Kinney et al., 2009), brainstem serotonergic deficiency cannot sufficiently explain the pathophysiology of SIDS. There may be a missing link to look for in the activating function of astrocytes of neuronal pacemaker circuits in the brainstem (Mitterauer et al., 2000).

Already in 2002, we published the hypothesis that mutations in genes required for proper functioning of the neuronal pacemaker circuits generating cardiorespiratory rhythms will predispose an infant to SIDS, and that mutations in clock genes may indirectly disturb cardiorespiratory function as well. In addition, mutations in astrocytes that modulate neurons in neuronal pacemaker circuits may impair cardiorespiratory rhythms (Mitterauer et al., 2000).

After a decade of further research on gliobiology, I now propose a specification of the possible role of astrocytes in SIDS. Given the well established modulatory function of astrocytes in synaptic neurotransmission, the deficiency in the serotonergic system of the brainstem may not be caused by a decreased synthesis, but by a relative lack of 5-HT and TPH2 because of an overexpression of serotonergic receptors on astrocytes, as already hypothesized (Mitterauer, 2010). Since the serotonergic system plays a crucial role in the control and homeostasis of the respiratory, cardiovascular, and autonomic systems, a significant decrease of serotonin may cause a severe disturbance of the rhythms generated by neuronal pacemaker circuits. This may be fatal in the critical developmental period during infancy.

In our 2000 hypothesis we also conjectured that intercellular calcium oscillations in astrocytes (Pasti et al., 1997), if disturbed, could affect synaptic cleft calcium concentrations and subsequently the amount of neurotransmitter released from presynaptic terminals. Although the function of spontaneous astrocytic oscillations in glia-neuronal interactions is unknown, it could shed some light on the pathophysiology of SIDS.
Given the fact that the brainstem houses a centre existential for life, where heartbeat and breathing is generated , spontaneous astrocytic pulsations may be essential for keeping up the activity in neuronal pacemaker circuits. Although the periods of astrocytic pulsations are slower than for instance the heartbeat (range 7-20 seconds), this is not contradictory. Glial rhythmic pulsations may exert an elementary vital function of the brain, at a lower level to guarantee survival, at a higher level to mediate interactions between the glial syncytium and the neuronal execution systems (Mitterauer, 2007).
Hence, a significant specification of our 2000 SIDS hypothesis is this:
If mutations affect genes responsible for the spontaneous astrocytic activity causing a severe disturbance of rhythmicity or even interrupting it- additionally impaired by stress- neuronal pacemaker circuits loose their function leading to death.
I am afraid that without referring to glia, research on SIDS will remain in a stalemate.

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