Neuronal nicotinic acetylcholine receptors: not just in brain

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The report from Fu et al., one of the current articles in focus (Ref 7, see page L1203 in this issue), shows the presence and functional activity of nicotinic acetylcholine receptors (nAChR) in neuroepithelial bodies (NEB) in neonatal hamster lung. NEB are small groups of pulmonary neuroendocrine cells (PNEC) located in airway epithelium typically at bifurcations of small airways. NEB appear to be chemo- and mechanoreceptors, and their numbers increase during midgestational lung development (5, 23). NEB synthesize a large variety of neuropeptides, growth factors, and vasoactive substances, including serotonin, and are thought to play a trophic role during lung development (23). The identification of active nAChR by Fu et al. (7) in NEB suggests mechanisms by which smoking during pregnancy impairs normal lung development, begins to help explain the link between smoking during pregnancy and sudden infant death syndrome (SIDS), and even has suggestions for the link between smoking and lung cancer.

Infants whose mothers smoke during pregnancy show diminished lung function, increased respiratory illness, increased asthma, and an increased chance of dying from SIDS (11, 24, 28). Indeed, smoking during pregnancy is now the most significant preventable cause of SIDS. In pregnant smokers, nicotine levels in amniotic fluid range from 5 to 200 nM, similar to, or slightly higher than, average plasma nicotine levels (1, 15). Given this, the expression of nAChR in lung during development provides a receptor-mediated mechanism to understand at the molecular level how smoking affects lung development. nAChR have previously been reported in airway epithelium (17, 20), fibroblasts (20), and type II cells (20). In airway epithelium, α7, α4β2, and other heteromeric nAChR forms have been reported (17, 20), and α7 nAChR have been reported in lung fibroblasts.

In Fu et al. (7), the authors have shown the presence of nAChR α3β2, α4β2, α7, and β2-subunits in NEB. These subunits form active nAChR with both fast-desensitizing currents, consistent with α7 homomeric nAChR, and slow-desensitizing currents, consistent with α4β2 or α3β2 heteromeric nAChR. These receptor subtypes all respond to nicotine at the concentrations present in amniotic fluid, and, therefore, the ability of nicotine transferred across the placenta to modulate nAChR activity in the developing lung is clear. Nicotine has also been shown to induce secretion from PNEC. Thus nicotine can directly affect lung development by interacting with nAChR on airway epithelium and fibroblasts and indirectly by stimulating release of trophic factors from NEB. This provides a mechanism by which smoking during pregnancy affects lung development and leads to the well-documented diminished pulmonary function in exposed infants at birth. Consistent with this, prenatal nicotine exposure alters lung structure in animal models (16, 20) in ways similar to changes seen in lungs of infants whose mothers smoked during pregnancy (6). It has also been suggested that nicotine-induced secretion of bioactive compounds from NEB may play a role in the increase of childhood asthma associated with maternal smoking (14).

Harder to understand has been the link between smoking and SIDS. SIDS likely results from a number of different disorders, ranging from cardiac defects to defects in respiratory patterns and regulation to impaired neonatal arousal responses (12, 26). The altered respiratory patterns or arousal responses could reflect defects in chemosensory signaling. Work from Youngson et al. (29) and others have clearly established that NEB are oxygen sensors and respond to hypoxia by changes in electrical activity and by increased release of serotonin and other factors (8). NEB are complexly innervated with vagal afferents (2), and alterations in NEB signaling will thus lead to altered signaling in the brain stem. The demonstration in the present paper by Fu et al. (7) of active nAChR in NEB now provides a clear mechanism by which nicotine can affect both local NEB secretory function and NEB signaling pathways. Consistent with this, Hafstrom et al. (9, 10) have shown that prenatal nicotine exposure alters breathing patterns and decreases response to hypoxia in newborn lambs, and Slotkin et al. (21) have showed altered responses to hypoxia in rats exposed to nicotine in utero. This is also consistent with the alterations in responses to hypoxia observed in β2 nAChR knockout mice (4). Particularly intriguing, given the release of serotonin by NEB in response to hypoxia, is the recent report of the increased risk of SIDS associated with polymorphisms of the serotonin transporter gene (27) that would be expected to increase serotonin reuptake.

However, although the expression of nAChR in NEB is highly intriguing, there is still little known about how nicotine actually links to SIDS. Is the site of action at the NEB, at other chemoreceptors, or in the brain...
stem, or are the effects additive? Are the effects neu-
ronally mediated or caused by humoral factors secreted
from NEB? Even more basic is the question as to
whether chronic nicotine leads to receptor activation or
desensitization. Surprisingly, such a basic question is
still highly controversial. In some systems, nicotine
clearly inactivates, as shown by desensitizing currents
in the present report (7) as well as in multiple other
studies (18). On the other hand, in some systems,
nicotinic receptors do not deactivate, as described by
Kawai and Berg (13) and Buisson and Bertrand (3). Of
course, it may be that the effects of prenatal nicotine
exposure are a complex mixture of receptor activation
and inactivation.

Finally, nicotine does not just affect NEB before
birth. Nicotinic receptors have been reported in small
cell lung carcinomas (SCLC), which are tumors derived
from PNEC or related precursor cells. SCLC express
neural tissue, such as lung, provides yet more rea-
son for sleep-disordered breathing after nicotine exposure.

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