TOXICOLOGICAL HIGHLIGHT

Screening for Developmental Toxicity of Tobacco Smoke Constituents

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The article highlighted in this issue is “Growth and Angiogenesis Are Inhibited in Vivo in Developing Tissues by Pyrazine and Its Derivatives,” by Goar Melkonian, Holly Eckelhoefer, Melinda Wu, Yuhuan Wang, Cathy Tong, Karen Riveles, and Prue Talbot (pp. 393–401).

Cigarette smoking is unrivaled among developmental toxicants in terms of total adverse impact on the human population. According to the American Lung Association, smoking during pregnancy is estimated to account for 20–30% of low-weight babies, up to 14% of preterm deliveries, and about 10% of all infant deaths (http://www.lungusa.org/tobacco/pregnancy_factsheet99.html). Both active (Stillman et al., 1986) and passive smokers (Martin and Bracken, 1986) have babies with lower than normal birthweights. The long-term consequences associated with low birthweight are just beginning to come to light, and they are many. Risks of childhood and adult morbidity, including—but not limited to—diabetes, cardiovascular disease, obesity, and cancer, are inversely related to birthweight (for review, see Godfrey and Barker, 2001; Slikker and Schwetz, 2003). It has been estimated that 12–24% of pregnant women smoke, with the lower figure coming from surveys based on self-reporting. Smoking is the single largest preventable risk factor for pregnancy-related morbidity and mortality in the US (Dempsey and Benowitz, 2001), and the Surgeon General’s Report (USDHHS, 2001) states that the known adverse women’s health effects of smoking “compels the Nation to make reducing and preventing smoking one of the highest contemporary priorities for women’s health.”

Vasculogenesis and angiogenesis are essential for embryonic development (Drake, 2003), and disruption of these processes can be a powerful mechanism of teratogenesis. In fact, thalidomide, the most notorious of human teratogens, may work at least in part through its known antiangiogenic properties (Ng et al., 2003; Stephens et al., 2000). In this issue,

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Melkonian and coworkers present another in a series of papers from their group demonstrating that constituents of tobacco smoke are developmentally toxic and antiangiogenic in the chick chorioallantoic membrane (CAM) assay. The use of the CAM to study effects on angiogenesis is well established, if not yet well standardized (Ribatti and Vacca, 1999; Richardson and Singh, 2003), and the signaling pathways controlling vasculogenesis and angiogenesis are highly conserved across species (Drake, 2003). The type of screening done in this paper demonstrates the advantages of screening systems when used appropriately in a mechanism or mode of action framework. Previous papers from the same group presented CAM assay results for pyridines identified in tobacco smoke (Ji et al., 2002) as well as for mainstream and sidestream tobacco smoke solutions (Melkonian et al., 2000, 2002). Pyridine derivatives with single methyl or ethyl substitutions were the most potent, inhibiting CAM growth down to picomolar concentrations. Both mainstream and sidestream cigarette smoke solutions caused abnormal pattern formation of CAM blood vessels and altered the composition of the extracellular matrix in the CAM mesoderm. In the paper highlighted here, the effects of pyrazine and derivatives previously identified in tobacco smoke are examined. Pyrazine itself was found to be a more potent inhibitor of CAM and embryo growth (picomolar concentrations) than any of the six derivatives tested. Effects on growth were apparently due to inhibition of cell proliferation, as DNA synthesis was inhibited by pyrazine. While higher concentrations inhibited angiogenesis and blood vessel pattern formation, these parameters were not affected at the lowest concentration that affected CAM and embryo growth. Since they previously demonstrated that tobacco smoke extracts were antiangiogenic, the authors speculate that there may be other, as yet untested, compounds in cigarette smoke that are more strongly antiangiogenic than is pyrazine. Yet the potency of pyrazine in this developmental assay is important, particularly in light of its inclusion on a list of chemicals that are generally regarded as safe additives for human foods and consumer products (Adams et al., 2002; Smith et al., 2001). Further work on its developmental toxicity is certainly merited.

Given the immense deleterious health effects of cigarette
smoking, there is a stark paucity of experimental data on the developmental toxicity of smoke constituents, of which there are more than 3000 (Hoffmann et al., 1997). Nicotine and carbon monoxide have received the bulk of the attention in this regard, and are certainly both developmental toxicants (Dempsey and Benowitz, 2001; Levin and Slotkin, 1998). Further screening of other cigarette smoke components would be of benefit in reducing tobacco-related developmental toxicity. Unfortunately, cessation programs to date have had only limited success. While cessation is the ultimate goal, benefits may also result from reductions in the levels of nicotine and other harmful constituents. Continued work is needed to identify the most deleterious compounds in mainstream and environmental tobacco smoke.

The Public Affairs Committee of the Teratology Society is drafting a Position Statement on the Importance of Smoking Cessation during Pregnancy, which will be published in an upcoming issue of Birth Defects Research. It is the committee’s position that the US must make the reduction of women’s smoking during pregnancy one of the highest priorities for fetal and child health. Experimental work to help elucidate the mechanisms and pathogenesis of smoking-related developmental morbidity is also needed to guide other potential forms of intervention and treatment.

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REFERENCES


