

## Airway relaxant may help asthma sufferers

Researchers have uncovered a natural bronchodilator that protects mice from asthma, offering a new target for treating the potentially fatal condition.

Difficult breathing associated with airway hyperresponsiveness and chronic inflammation characterizes asthma, which affects 15 million Americans, including ~5 million children. Asthma research has generally focused on elucidating the mechanisms that cause the airways to constrict, and has devoted little attention to the idea that the problem may actually lie in the inability of the airways to relax following constriction. Now, a research team led by Jonathan S. Stamler, a professor of medicine at Duke University Medical Center (Durham, NC), has shown in mice that failure of affected airways to relax may be more important to the pathology of an asthma attack than previously thought.

Although nitric oxide (NO) is thought to regulate airway tone, researchers have not been able to affect allergen response

by manipulating NO levels in mice. Stamler's group looked at the role of an NO-carrying compound, S-nitrosoglutathione (GSNO), on airway constriction and dilation (*Science*, 10 June).

When challenged with an allergen, the airway lining fluid of wild-type mice prone to asthma showed reduced levels of GSNO, associated with elevated levels of GSNO reductase (GSNOR), the enzyme that breaks down GSNO. Challenge with a control substance (PBS) did not result in detectable levels of GSNOR in the airway lining fluid. On the other hand, GSNOR knockout mice, which do not produce the enzyme, show elevated levels of GSNO and do not develop asthmatic symptoms when exposed to an allergen.

This study also calls into question the traditional notion that inflammation has a role in the pathogenesis of asthma. Stamler's team found comparable inflammatory responses, characterized by the presence of eosinophils, interleukin-13, and IgG antibodies, in wild-type and



GSNOR knockout mice exposed to PBS or allergen.

Finding ways to increase GSNO levels, either by administration of the compound or inhibition of GSNOR, may lead to new ways to treat asthma in humans. Stamler tells *Lab Animal* that the group's future plans include "assessment of GSNO/GSNOR levels in asthmatic patient populations, search for inhibitors of GSNOR, and hopefully test[ing of] GSNO in clinical trials."

**Tanja Schub**

### UNRAVELING THE MYSTERIES OF ENVIRONMENTAL CANCER RISK

New research in rats has uncovered evidence that environmental variables can specifically exacerbate the risk of certain cancers in genetically predisposed individuals in surprising ways.

It's pretty common knowledge that there are plenty of chemicals out there capable of wreaking havoc on unsuspecting DNA; likewise, the role of genetics in the eventual emergence of cancer and other diseases is well established. Less well understood, however, is the manner in which environment and genetics can collude to increase risk of disease—a mystery that scientists are just starting to unravel.

"Among individuals with genetic defects that predispose them to cancer as adults, not all of those individuals develop cancer. It can vary tremendously, even for people who have the exact same mutation," explains Cheryl Lyn Walker of the MD Anderson Cancer Center (Houston, TX). Environmental variables may be the key, and there is considerable evidence, she says, supporting a model of 'developmental programming', in which external factors modulate genetics in a mutation-independent fashion.

To further explore this phenomenon, Walker and her colleagues examined the effects of diethylstilbestrol (DES), an estrogenlike drug formerly prescribed to prevent miscarriage. Women exposed to DES *in utero* often develop abnormalities of the reproductive tract and increased risk for cervical-vaginal cancer. Walker's group worked with the Eker rat, a strain heterozygous for a mutation that predisposes them to develop uterine leiomyomas,

exposing neonatal rats to DES and observing the compound's effects (*Proc. Natl. Acad. Sci. USA*, 14 June).

Diethylstilbestrol caused developmental abnormalities in the reproductive tracts of both Eker and wild-type rats. However, only the Eker rats showed an increased cancer risk: Eker rats normally show 64% tumor incidence, but neonatal DES exposure raised that risk to 92%. Their tumors also appeared in greater numbers and were considerably larger. Strikingly, DES did not affect the frequency with which Eker rats developed a second, cancer-causing mutation; what changed was the penetrance of that cancer phenotype. DES-treated rats also showed elevated expression of certain genes in response to estrogen signaling. These last two pieces of evidence suggest that DES may amplify cancer risk by direct modification of the chromosomal DNA at estrogen-regulated genes, a proposal Walker's team is now exploring.

Walker suggests that virtually any hormone-driven cancer could be a potential target for this process, and that some tissues with longer developmental spans could be at greater risk. "For the breast, the window would be huge, from before birth until your first-term pregnancy—so for the breast, you could imagine a vulnerability to environmental exposures that's very long lasting," she says. "We are glad that this story is getting out there, because it's really important when we consider risk that we look at the entire life span of the individual, not just their adult or occupational exposure."

**Michael Eisenstein**