Possible pharmacological target(s) identified in pediatric OSA

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Children with obstructive sleep apnea (OSA) may one day be able to have an injection or use a throat spray instead of getting their tonsils removed to cure their snoring, according to a new study from the University of Chicago, which found that a specific gene product may be responsible for the proliferation of adenotonsillar tissue that can cause pediatric OSA.

"We found that in the tonsil tissues of children with OSA, certain genes and gene networks were over expressed," said David Gozal, M.D., professor and chair of the Department of Pediatrics, who led the study. "We believe that the results of this gene overexpression is increased proliferation of the adenotonsillar tissues, which in turn can cause partial or complete obstruction of the upper airways during sleep."

The findings have been published online ahead of print publication in the American Thoracic Society's *American Journal of Respiratory and* Critical Care Medicine.

In the United States, two to three percent of children have OSA. The current standard of treatment is surgical removal on the tonsils, but surgery is not without risks and potential complications. Currently, about 600,000 tonsillectomies are performed each year in children, primarily to treat OSA.

Dr. Gozal and colleagues have been studying potential non-surgical alternatives to treat OSA in children. To identify potential

pharmacological targets, they recruited 18 children with OSA and 18 age-, gender-, and ethnicity-matched children with recurrent tonsillar infections (RI), all of who underwent surgery to have their tonsils removed.

The tonsil tissue from each subject was analyzed for relative expression of the 44,000 known genes in the human genome. The researchers then further analyzed the gene pathways to determine which changes may represent differences with a high likelihood of impact on cellular proliferation.

"We wanted to find the most important and functionally pertinent genes, those with the most connectivity," explained Dr. Gozal. "We identified 47 genes and among those, two specific genes, both phosphatases, which are known to be very important at regulating communication in cells. Then we looked at the expression of the phosphatase protein and found that children with OSA have higher level of phosphatases in the tonsils." In particular, they focused on one protein called phosphoserine phosphatase (PSPH) that was expressed in children with OSA, but almost never expressed in the children with RI.

"We asked, 'What happens if we block this phosphatase?'" said Dr. Gozal. "Is this a potential target for pharmacological therapy?" Indeed, they found that introducing calyculin, a phosphatase inhibitor, reduced the cell proliferation and increased programmed cell death, or apoptosis, a process by which cells self-regulate, in the tonsils of OSA patients. "Together, these observations suggest that PSPH is a logical therapeutic target in reversing adenotonsillar enlargement in pediatric OSA," Dr. Gozal wrote.

"The next direction is to identify if selective clones of proliferating cells that may be affected by PSPH or by another of the discovered target genes with the intent of developing a non-surgical alternative treatment

to surgery for OSA in children," said Dr. Gozal. "If there is a subgroup of cells that have specific markers, then we may be able to develop a therapy that could be specifically targeted to these cells."

"Phosphatases such as PSPH are an exciting prospective target for therapy in children with OSA," said Dr. Gozal. "We believe if we had effective non-surgical alternatives to tonsillectomies, it would be of great benefit."

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