Puberty Mystery Solved

A 100-year-old hypothesis that a secretion of the pineal gland suppresses puberty is shown to be correct; but that secretion, melatonin, has other mysteries

For nearly a century, medical scientists have speculated that the onset of puberty might be triggered by a decrease in secretions from the pineal gland—a small white pinecone-shaped structure buried in the center of the brain. They did hundreds of experiments, grinding up hundreds of thousands of pineal glands, but, until recently, the question was still open. Now a group of researchers from Massachusetts Institute of Technology (MIT) and Austria has determined that the old hypothesis is correct, thus closing a chapter of medical history. At the same time, however, they are opening a new chapter. The pineal secretion—which is the hormone melatonin—may help determine daily rhythms and may be one reason that children sleep so much more than adults. It remains a challenge to tie together these multiple functions of the substance.

The melatonin story began in 1898 when Otto Heubner, a German physician, published a case report of a 4-year-old boy with precocious puberty. The boy died and on autopsy Heubner found that a brain tumor had invaded and destroyed his pineal gland. Heubner reasoned that perhaps the pineal gland of children normally produces a substance that actively suppresses puberty.

Heubner's hypothesis was controversial but fascinating to the medical community. Hundreds of papers were published in attempts to prove or disprove it. In 1954, Julian Kitay and Mark Altschule of Harvard Medical School surveyed the entire world literature on the pineal gland and reported that of the 1800 publications, about half dealt with the puberty question. But still there was no clear answer. Kitay and Altschule concluded that the pineal probably has something to do with puberty, but whatever it does is pretty subtle.

Shortly after Kitay and Altschule's survey, investigators discovered that if they removed the pineal gland from immature rats, the rats' gonads grew bigger; if they gave extracts of cattle pineals to other rats, the cattle pineals suppressed the growth of the rat gonads.

The next clue came in 1959 when Virginia Fiske of Wellesley College asked how light affects the brain. She put a group of rats in continuous light and put another group in continuous darkness. When she killed the animals and looked for changes in their brains, the only difference she could find was in the pineal gland. The rats kept in the dark had slightly larger glands than those kept in light. It had already been shown that light affects the gonads. When female rats are kept in continuous light, for example, their ovaries get larger and their estrus cycles get shorter. One possible explanation of these findings is that light suppresses the pineal and the pineal suppression affects the gonads.

But still it was not clear just *what* about the pineal was being suppressed. Then, at about the same time that Fiske was doing her experiments, Aaron Lerner, a Yale dermatologist, did experiments that led him to discover the pineal hormone melatonin.

Julius Axelrod of the National Institutes of Health became interested in melatonin and discovered that it is synthesized from *N*-acetylserotonin by the enzyme hydroxyindole-*O*-methyltransferase (HIOMT). Richard Wurtman, who is now at MIT, worked with Axelrod in the early 1960's and postulated that melatonin is the pineal substance that inhibits the gonads and that the synthesis of melatonin is suppressed by light and stimulated by darkness.

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But at that time no one could measure melatonin directly—the assays were not sufficiently sensitive. What they could measure was the enzyme HIOMT and that enzyme, they learned, is present in greatest quantities in the pineals of animals kept in the dark.

About 10 years ago, Harry Lynch of MIT developed a good assay for melatonin in urine and found that there are daily rhythms of the hormone in humans. As expected, the hormone is produced in maximal amounts at night. At that point, a number of investigators decided to look again at the puberty hypothesis. But the problem, says Wurtman, is that they sampled blood and urine during the day rather than at night and they looked at samples from children aged 10 or 11. By that age, Wurtman says, "It is already too late. If a drop in the secretion of melatonin is to trigger puberty, that drop has to occur before the early endocrine changes of puberty, which means the children have to be no more than 7 or 8 years old."

Last year, Franz Waldhauser of Universitaets-Kinderlinik in Vienna, Austria, came to Wurtman's lab as a postdoctoral fellow, planning to look once more at the puberty hypothesis. "Waldhauser collected blood samples from kids in Vienna, starting at very young ages. He came with a freezer full of this blood," Wurtman says. Because these samples were from hospitalized children, Waldhauser was able to obtain them at night, when melatonin is synthesized. The MIT scientists found a striking decrease in melatonin synthesis as the children's ages increased. Melatonin levels were highest in the children aged 1 to 5 and decreased steadily until the end of puberty. By the end of puberty, the peak melatonin levels have decreased 75 percent from their values early in childhood. Melatonin concentrations in the daytime were uniformly low and bore no relationship to the ages of the children.

This correlation between a decrease in melatonin synthesis and the onset of puberty does not, of course, prove that melatonin itself suppresses puberty. But it certainly is consistent with the hypothesis. The melatonin story, however, is far from over. The hormone, Wurtman points out, probably has several functions. For example, there is new evidence that it affects behavior. Harris Lieberman of MIT administered it to male volunteers in the daytime. The hormone, he finds, made the men sleepy. Does this explain why children, who make so much more melatonin than adults, need so much more sleep? "No one would put up an argument against that hypothesis," Wurtman remarks. But, he notes, the effects of melatonin are only beginning to be explored. The hormone's secretion varies with the seasons and with light and dark. How it affects sexual maturation is still a mystery. How it affects behavior is largely unknown. Yet, he says, there is something quite satisfying in resolving at last Heubner's hypothesis of the past century.—**Gina Kolata**