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The Pineal Gene Expression Party: Who's the Surprise Guest?

Every night there's a gene expression party in the rodent pineal gland. And, the party just became a lot more interesting, with a report from the pineal group headed by Tony Ho in Edmonton, as described in the current issue of *Endocrinology* (1).

The gene expression party in the rodent pineal gland is linked to the main function of the pineal gland, the generation of a circadian rhythm in circulating melatonin. The pineal gland is a melatonin factory and the factory is turned on and off on an approximately 24-h basis. One of the functions that is turned on is the expression of many genes. Among these rhythmically expressed genes, the best studied is *arylalkylamine N-acetyltransferase (aanat)* (2), which encodes the next to last enzyme in melatonin synthesis. Every night the abundance of *aanat* mRNA increases more than 100-fold within a few hours!

This increase is driven by the master circadian clock in the suprachiasmatic nucleus, which sends stimulatory signals to the pineal gland at night by way of a neural circuit. This causes the release of norepinephrine in the pineal gland, which binds to membrane-associated adrenergic receptors, causing an elevation of the concentration of cAMP. cAMP in turn activates cAMP-dependent protein kinase A (Fig. 1). It has been presumed that it activates *aanat* transcription by simply phosphorylating a protein, termed cAMP response element binding protein (CREB), which acts by binding to short sequences in the *aanat* gene described as cAMP regulatory elements. Workers in the field have thought that phosphorylation of CREB alone was responsible for the activation of *aanat* transcription (2).

The same mechanism has been suspected to activate transcription of other cAMP-regulated genes in the pineal gland, including *type II thyroxine deiodinase* (3), *MAPK phosphatase1* (4), *methionine adenosyl transferase* (5), *fos-related antigen-2* (6), *oligopeptide transporterPepT1* (resulting in a pineal-specific isoform) (7), *NFGI-B (8)*, *RZR(ROR)β* (9), *phosphodiesterase 4B2* (10), *inducible cAMP early repressor* (11), and α_{1b}*-adrenergic receptor* (12).

However, the view that a single mechanism mediates cAMP activation of gene expression may now have to be revised in light of the findings in the report by Ho and his co-workers (1).

This group has discovered that another DNA binding protein appears to play a global role in the pineal gene expression party. The mystery guest is histone H3. Histones are well-characterized and extensively studied proteins that bind to DNA and form chromatin, the condensed form of nuclear DNA. Phosphorylation of histones is known to cause remodeling of chromatin, opening up the condensed mass of DNA, thereby enhancing the likelihood that a transcription factors will find its own specific regulatory element.

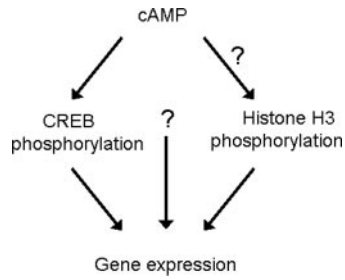

FIG. 1. cAMP control of pineal gene expression. The second messenger controlling expression of many genes in the pineal gland is cAMP, which is regulated by norepinephrine. cAMP controls expression of some genes in the pineal gland through phosphorylation of CREB. cAMP also elevates the phosphorylation of histone H3 through unknown mechanisms. This is likely to enable expression of many other genes, perhaps by enhancing access of transcription factors in the pinealocyte to regulatory elements of target genes.

The Edmonton group found that phosphorylation of a specific residue on histone H3—serine 10—increases robustly every night. The only other tissue in which this is known to occur on a circadian basis is the suprachiasmatic nucleus (13). The large changes in the phosphorylation state of pineal histone H3 were also found by the Ho team to be rapidly reversed when neural stimulation is terminated; dephosphorylation reflects the action of unidentified protein phosphatases.

The evidence that H3 phosphorylation exhibits a 24-h rhythm suggests it may play a global role in controlling circadian changes in the expression of the pineal transcriptome. In contrast to the selective interaction of phosphorylated CREB (pCREB) and cAMP regulatory elements, H3 phosphorylation may have a broad nonspecific permissive effect by facilitating the action of pCREB and many other transcription factors by enabling access to regulatory elements in genes.

The H3 phosphorylation story raises many fascinating questions: Can pCREB promote expression of *aanat* in the absence of H3 phosphorylation? Are there specific kinases in the pineal gland that mediate cAMP-dependent phosphorylation of H3? Is H3 phosphorylation also influenced by other factors? Do other modifications of histones, including methylation and acetylation, play a role in circadian gene expression in the pineal gland? Do other transcription factors rely on H3 phosphorylation to induce gene expression at night?

The pineal H3 phosphorylation finding emphasizes how little is known about the mechanisms that control the pineal

Abbreviations: CREB, cAMP response element binding protein; pCREB, phosphorylated CREB.

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gene expression party. Certainly, it would now appear that we can no longer assume that cAMP-dependent phosphorylation of CREB is the entire story. This exciting advance opens up many new novel opportunities for investigation of gene expression in the pineal gland and is expected to have broad influence on future research in this area.

David C. Klein
Section on Neuroendocrinology
Office of the Scientific Director
National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, Maryland 20892

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Address all correspondence and requests for reprints to: Dr. David C. Klein, Section on Neuroendocrinology, Office of the Scientific Director, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20892. E-mail: kleind@mail.nih.gov.

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