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LETTER

Clock genes as a link between addiction and obesity

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In their recent News and Commentary article, Yuferov *et al*[1] reviewed the evidence for a role of clock genes in modulating drug addiction. They focused on findings in *Clock* mutant mice.[2] These mice do not have a functional CLOCK protein (a transcription factor that may regulate the expression of genes with E-box sequences in their promoters) and they express increased reward behaviors in response to cocaine. However, another important phenotype of *Clock* mutant mice, which may be relevant for drug addiction has not been mentioned. These mice also suffer from obesity and have a serious metabolic syndrome.[3] It has already been inferred that obesity and addiction may share common mechanisms. The fact that *Clock* mutant mice are models for both addiction and obesity may be interpreted as evidence that clock genes participate in brain mechanisms that regulate eating and cocaine addiction (eg, pleasure); for example, through a dopamine neurotransmitter system.[2] However, an alternative explanation may be that the peripheral action of clock genes, for example on adipose cells, is the common mechanism. Shimba *et al*[4] reported that another clock gene product, BMAL1, which acts in concert with CLOCK as a transcription factor, directly regulates lipogenesis. Alterations in the metabolism of fatty acids may significantly modulate the behavioral effects of cocaine.[5] Since fat metabolism and fatty acids may prominently influence neuronal functioning, it is possible that *Clock* mutants have an altered cocaine responsiveness, due to both the central and peripheral sites of clock genes action.

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References

1 Yuferov V, Butelman ER, Kreek MJ: Biological clock: Biological clocks may modulate drug addiction. *Eur J Hum Genet* 2005; **13**: 1101–1103.
2 McClung CA, Sidiropoulou K, Vitaterna M *et al*: Regulation of dopaminergic transmission and cocaine reward by the *Clock* gene. *Proc Natl Acad Sci USA* 2005; **102**: 9377–9381.
3 Turek FW, Joshu C, Kohsaka A *et al*: Obesity and metabolic syndrome in circadian *Clock* mutant mice. *Science* 2005; **308**: 1043–1045.
4 Shimba S, Ishii N, Ohta Y *et al*: Brain and muscle Arnt-like protein-1 (BMAL1), a component of the molecular clock, regulates adipogenesis. *Proc Natl Acad Sci USA* 2005; **102**: 12071–12076.
5 Kurtuncu M, Battista N, Uz T *et al*: 5-Lipoxygenase gene disruption in mice alters their behavior, cocaine responsiveness, and the brain endocannabinoid system. Program No. 800.6, 2005 Abstract Viewer/Itinerary Planner. Washington, DC: *Society for Neuroscience, Online*.