Neurobiology of Sleep and Waking: Waking II

Chiara Cirelli, M.D., Ph.D.
Department of Psychiatry
University of Wisconsin/Madison

Waking systems: brain mechanisms of arousal

Anatomy of the Locus Coeruleus

modified from Jones B, SRS Basic of Sleep Guide

Carpenter's Human Neuroanatomy, 9th edition
Dendrites of Locus Coeruleus Neurons Extend Preferentially Into Two Periependymal Zones

Michael V. Murphy, Steven P. Fish, K. Robert Ennis, James E. Aston-Jones

Prefrontal cx
Amygdala
Lat hypothalamus
Dorsal raphe
PGI, PH

Foote et al., PNAS 77:3033-3037, 1980
Berridge and Abercrombie, Neuroscience 93: 1263-1270, 1999
**LC effects on EEG and behavior - 1**

- thalamus
- cortex
- NA, Ach, DA, 5-HT


**LC effects on EEG and behavior - 2**

- Pre-infusion
- Post-infusion
- Recovery


**LC effects on EEG and behavior - 3**

Darracq et al., Neuroreport 8: 351-355, 1996

sufficient?
Role of Ach and NE in maintaining EEG activation


The basal forebrain and arousal

Cape and Jones J Neurosci 18: 2653-2666, 1998

Serotonin, waking, and sleep

Dorsal raphe lesions cause insomnia in the cat. (Jouvet)

BUT......
- this insomnia is reversible
- 5-HT neurons are active during waking, not during sleep
- 5-HT may facilitate sleep by inhibiting the cholinergic system
Serotonin, waking, and sleep

**The Locus Coeruleus – Summary**

- NA is important, but neither necessary nor sufficient for waking/EEG activation
- NA acts through both alpha1 and beta adrenoceptors
- NA acts through thalamus, cortex, and basal forebrain, most likely by enhancing glutamatergic and cholinergic transmission
Waking systems: brain mechanisms of arousal

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The Histaminergic System

there is no high-affinity uptake system for histamine

Brown et al., Progress in Neuroradiol. 43: 627-673, 2001

Anatomy of the Histaminergic System

Histaminergic block increases sleep in cats

Panula et al., Neuroscience 28: 585-610, 1989

Anatomy of the Histaminergic System - 1


Anatomy of the Histaminergic System - 2

Lin et al., Brain Res 479: 225-240, 1989
Antihistamines

- first-generation: (e.g. hydroxyzine); have sedative effects, used for insomnia; lipophilic, easily pass the BBB; many also inhibit cholinergic (muscarinic), serotonergic and adrenergic (alpha1) transmission

- second-generation: do NOT have sedative effects (cetirizine?); hydrophilic, do not easily pass the BBB; highly selective for H1 receptors (anti-inflammatory)

- H2 receptor antagonists (e.g. ranitidine): in general do NOT have sedative effects (cimetidine?); do not easily pass the BBB; highly selective for H2 receptors (to block gastric acid secretion)

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The Histaminergic System

Histaminergic neurons are waking-specific
Histaminergic neurons are waking-specific

Histaminergic neurons are waking-specific

not necessary for waking up

HDC KO mice

Parmentier et al., J Neurosci 22: 7695-7711, 2002

Takahashi et al., J Neurosci 26: 10292-10298, 2006
Where does H act to cause arousal?

Histaminergic activation increases waking in cats

Histaminergic activation increases waking in cats
**Histaminergic activation increases waking in cats**

Lin et al., J Neurosci 16: 1523-1537, 1996

**Histamine in the CSF**

- H content in the cortex and thalamus of narcoleptic dogs is significantly reduced
- in humans, H content in the lumbar cerebrospinal fluid (CSF) is reduced in hypocretin-deficient narcolepsy, hypocretin non-deficient narcolepsy, and idiopathic hypersomnia
- May CSF histamine be a new biomarker for hypersomnias of central origin?
- H in CSF seems to reflect the previous sleep/waking history

*Aso et al., Neurosci Lett 430: 224-229, 2008*

**The Histaminergic system – Summary**

- H is important for maintaining, not for initiating waking
- H acts on waking/EEG activation through H1 receptors
- H probably acts in the thalamus, cortex, basal forebrain, and pontine tegmentum by enhancing glutamatergic and cholinergic transmission
The hypocretin system

Hypocretin 1 and 2

De Lecea et al., PNAS 95: 322-327, 1998