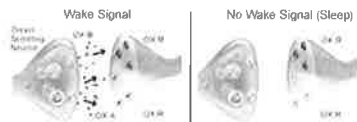




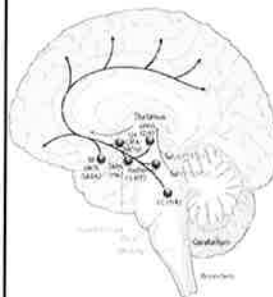
### Orexin Signaling Throughout the Day



Orexin signaling is active during wakefulness and falls silent during normal sleep

\*Extrapolated from rat and non-human primate data. Ethical methods of CSF assessment prevent accurate readings in humans. 1. Rankovic Z et al, eds. *Drug Discovery for Psychiatric Disorders*. Royal Society of Chemistry, 2012.

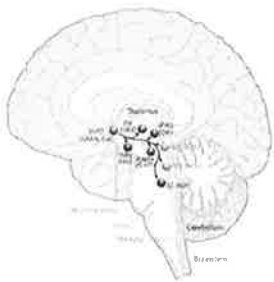
### Wake Promotion: Arousal Promoting Regions of the Brain



Locus	Neurotransmitter(s)
Pedunculopontine nuclei (PPT)	Acetylcholine (ACh)
Lateral dorsal tegmental nuclei (LDT)	ACh
Locus coeruleus (LC)	Noreadrenaline (NA)
Raphe nuclei	Serotonin (5-HT)
Ventrolateral periaqueductal gray (VPAG)	Dopamine (DA)
Tuberonammillary nucleus (TMN)	Histamine (His)
Lateral hypothalamus (LHA)	Orexin (ORX) or melanin-concentrating hormone (MCH)
Basal forebrain (BF)	γ-aminobutyric acid (GABA) or ACh

Saper CB et al. *Nature* 2005, 437, 1251-1263

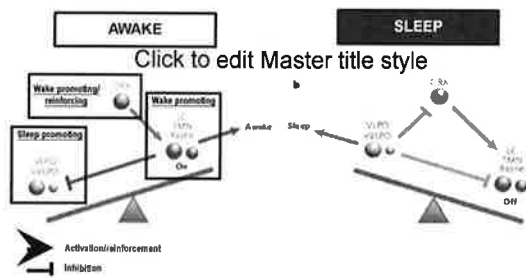
### Sleep Promotion: Ventral lateral preoptic nuclei (VLPO)



Locus	Neurotransmitters
Ventral lateral preoptic nuclei (VLPO)	γ-aminobutyric acid (GABA) and galanin

Saper CB et al. *Nature* 2005, 437, 1251-1263

### Saper's Flip-Flop Switch: Describing the Transitions Between Wake and Sleep



Saper CB et al. *Nature* 2005, 437, 1251-1263