Neurobiology of Sleep and Waking: Waking I

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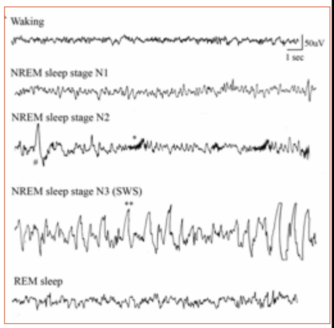
Sleep stages

"activated EEG"



Sleep stages

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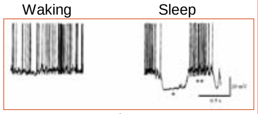
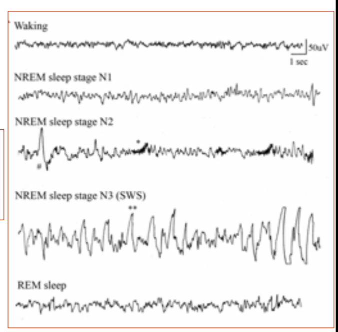
Waking Sleep



recording from a cortical neuron



EEG "activation" is associated with behavioral arousal

ELECTRICAL POTENTIALS FROM THE INTACT HUMAN BRAIN[1]

Dr. Hans Berger, of Jena, has published a series of papers in which he reports that changes in electrical potential which are correlated with human brain activity may be magnified and recorded by the use of a suitable vacuum-tube amplifying system and an oscillograph.[2] These potential changes are obtained from needle or surface electrodes placed on different points of the head. His most typical electrode ar-

In most of our experiments electrodes made of silver disks 1 to 2 c in diameter, covered with flannel soaked in salt solution, are used. These electrodes are placed on the skin surface and usually at opposite poles of the head. For example, one may be placed

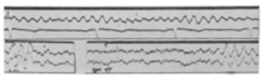


Fig. 1

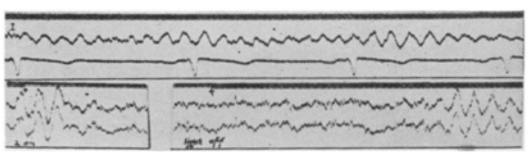
The first record of Fig. 1 shows the alpha waves in the upper line and in the second line a record taken, as a control, simultaneously from electrodes placed across the left leg above the knee. A record of the

The second record shows two recordings of the effect of light stimulation on the large alpha waves. The two records are taken across different parts of the head. It will be noted that these waves are markedly reduced by the light stimulation after a latency of 0.4 seconds. (The time line at the top of the record indicates 1/50 second intervals. The signal indicating the period of stimulation is marked by an upward deflection of the time line). When the light stimulus is turned off, the alpha waves return to normal after a short period. The duration

In conclusion, we may say it has been possible for us to confirm many of Berger's observational findings. With the improvement of recording techniques and with an increased understanding of the functional relationship between the results secured and other processes of the living organism, it may well be that electroencephalograms of the sort described in this note may prove significant in psychology and clinical neurology. It is even possible that this technique may provide information in regard to brain action which will be comparable in significance to the information in regard to heart function which is provided by the electrocardiograph. Further experimental studies of the phenomena described here are in progress.

H. H. Jasper
L. Carmichael

Science 81: 51-53, 1935



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Passive sleep and active sleep

Passive theories of sleep:

- Kleitman (1929, 1963)
- Bremer (1935, 1938)
- Moruzzi and Magoun (1949)

Active theories of sleep:

- Moruzzi (1972)
- Jouvet (1972)

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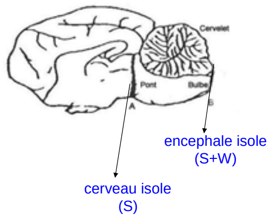

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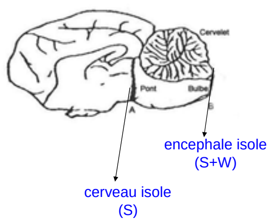
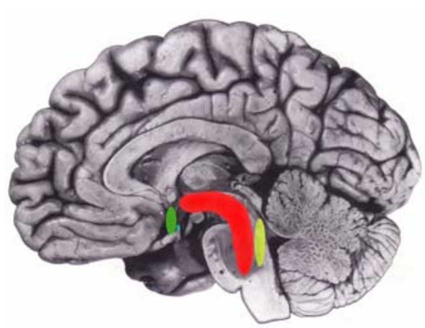
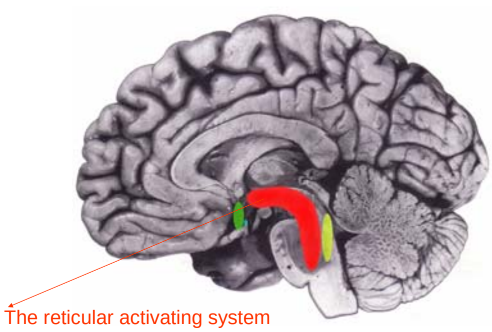


OR BOTH………..

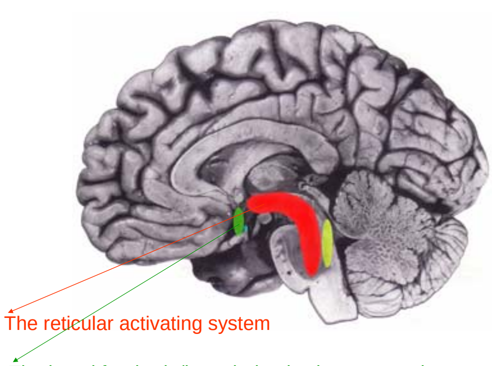
Sleep and Waking Systems



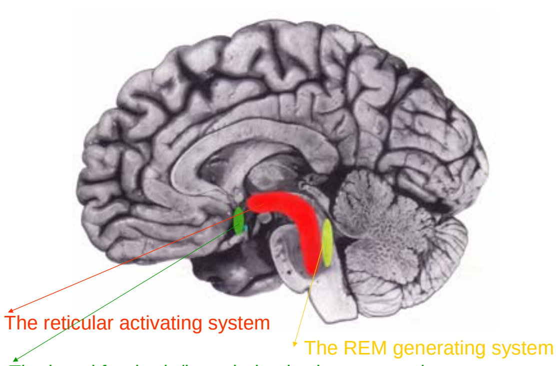
Sleep and Waking Systems



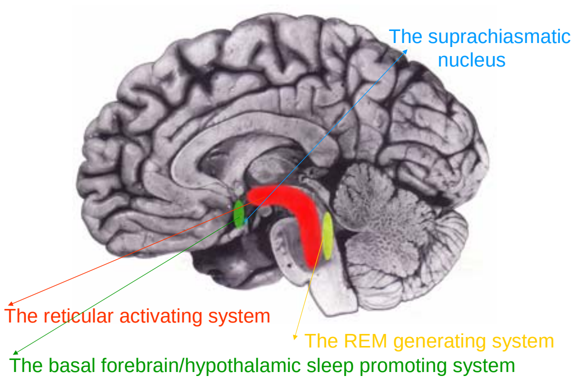
Sleep and Waking Systems



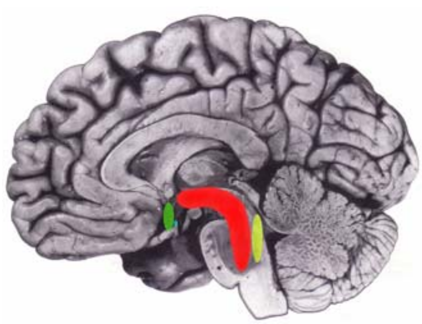
Sleep and Waking Systems



Sleep and Waking Systems

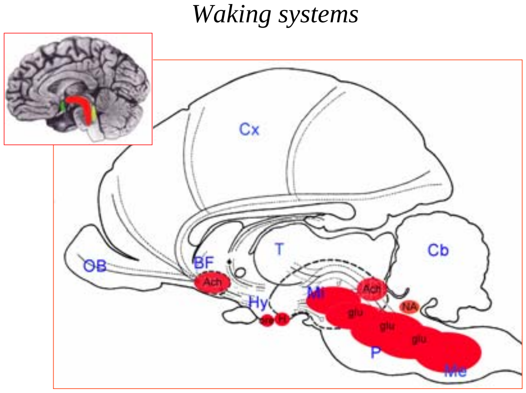


Centers or Systems?



…no sleep or wake state in toto can be said to have a center and even few, if any components of waking-sleep states have “a center”….
(Steriade and McCarley, Brainstem Control of Wakefulness and Sleep, p.21)

Waking systems



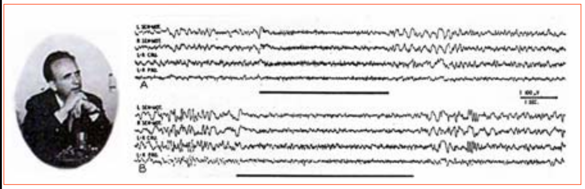
modified from Jones B, SRS Basic of Sleep Guide

The discovery of ARAS, the Ascending Reticular Activating System

COMMUNICATIONS

BRAIN STEM RETICULAR FORMATION AND ACTIVATION OF THE EEG [1]

G. Moruzzi, M.D. [2] and H. W. Magoun, M.D.
Department of Anatomy, Northwestern University Medical School



Moruzzi and Magoun, Brainstem reticular formation and activation of the EEG, EEG Clin Neurophysiol 1: 455-473, 1949

The discovery of ARAS, the Ascending Reticular Activating System -2

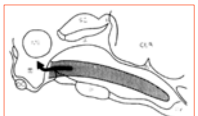
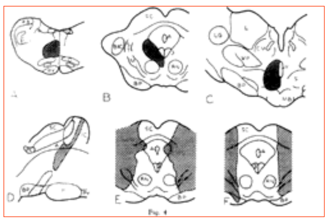


Fig. 3
Reconstruction of midsagittal plane of cat's brain stem upon which is projected, with cross-lining, the distribution of the ascending reticular activating system.
Abbreviations are as follows: A, aqueduct; CER, cerebellum; IC, inferior colliculus; MI, massa intermedia; OC, optic chiasma; P, pons; PY, pyramidal crossing; SC, superior colliculus; III, third ventricle; IV, fourth ventricle.



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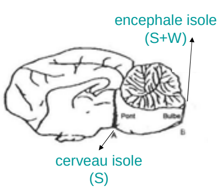
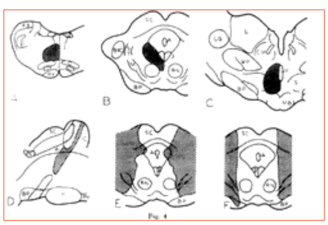
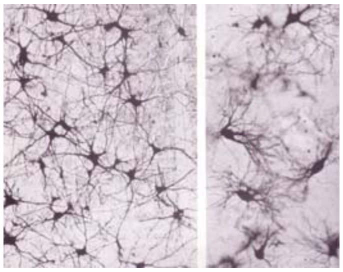
The discovery of ARAS, the Ascending Reticular Activating System -2

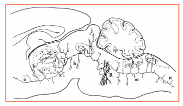


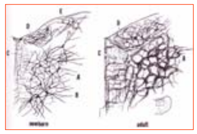


Moruzzi and Magoun, Brainstem reticular formation and activation of the EEG, EEG Clin Neurophysiol 1: 455-473, 1949

The Reticular Formation

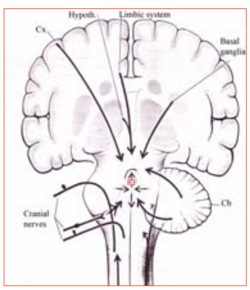




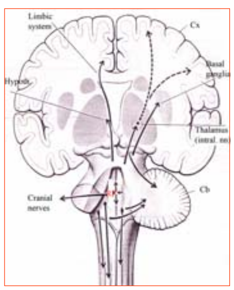


Scheibel and Scheibel, 1975

The Reticular Formation



afferents



efferents

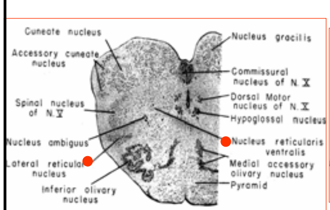
Carpenter's Human Neuroanatomy, 9th edition

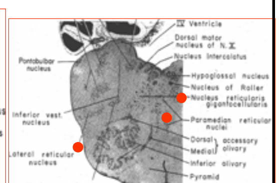
The Reticular Formation- medulla

Medullary RF:

- paramedian group (paramedian ret. N.)
- central group (ventral ret. N, gigantocell. ret. N)
- lateral group (lateral ret. N, parvicell. Ret. N)

ascending projections
to intralaminar th. NN
(central tegmental tract)





Carpenter's Human Neuroanatomy, 9th edition

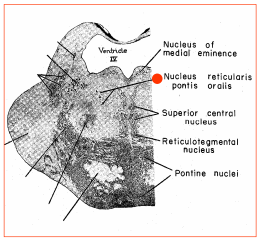
The Reticular Formation- pons

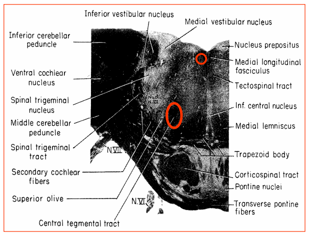
Pontine RF:

caudal pontine ret. N

oral pontine ret. N

ascending projections
via the central tegmental tract
and the medial longitudinal f.





Carpenter's Human Neuroanatomy, 9th edition

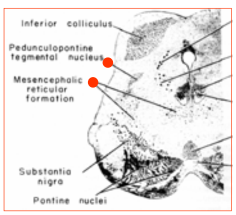
The Reticular Formation- midbrain

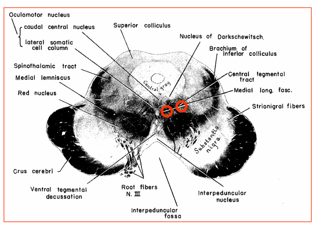
Midbrain (mesencephalic) RF:

pedunculopontine tegmental N

MRF

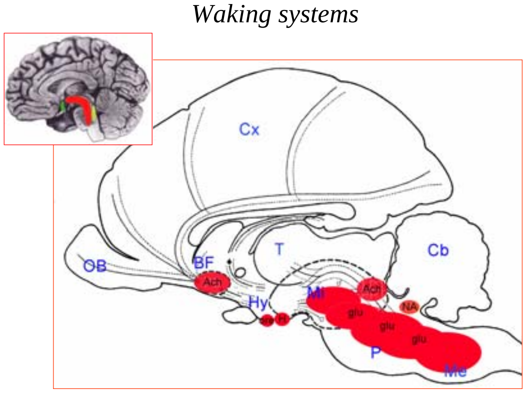
ascending projections
via the central tegmental tract
and the medial longitudinal f.





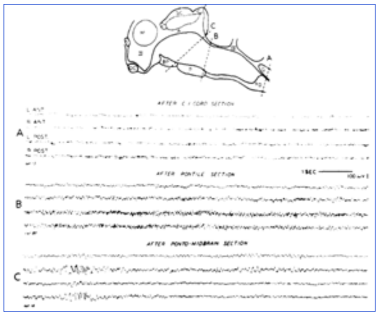
Carpenter's Human Neuroanatomy, 9th edition

Waking systems



modified from Jones B, SRS Basic of Sleep Guide

The discovery of ARAS, the Ascending Reticular Activating System -3



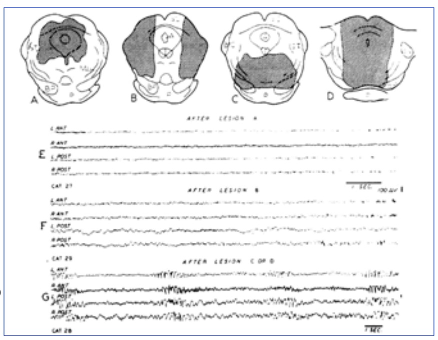
Lindsley et al., EEG Clin Neurophysiol 1: 475-486, 1949.

The discovery of ARAS, the Ascending Reticular Activating System -3

A

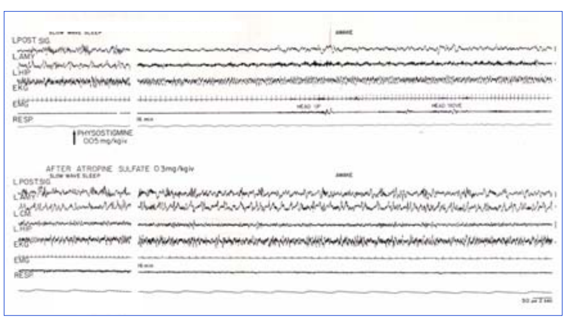
B

C or D



Lindsley et al., EEG Clin Neurophysiol 1: 475-486, 1949.

Arousal and the cholinergic system



Domino et al., Progr Brain Res 28: 113-133, 1968
Wikler A. Pharmacologic dissociation of behavior and EEG "sleep patterns" in dogs; morphine, n-allylnormorphine, and atropine. Proc Soc Exp Biol Med. 1952 Feb;79(2):261-5.

The cholinergic system and arousal

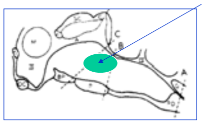
Table 1. Rate of liberation of acetylcholine from cerebral cortex during slow wave sleep (SWS), paradoxical sleep (PS), and waking (W). Expressed in nanograms per minute per square centimeter of cortical surface.

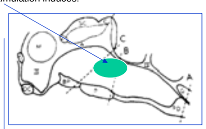
Exp.	Acetylcholine liberated SWS	PS	W
1	1.3	3.2	
2	2.0		3.5
3	1.7	3.1	3.3
4	1.2	3.1	2.5
5	0.4	0.9	0.7
6	1.1	2.0	1.9
7	1.0	1.5	1.2
8	1.1	1.9	1.9
9	1.0		1.9
Mean	1.2	2.2	2.1
S.D.	0.4	0.8	0.9

Jasper and Tessier, Science 172: 601-602, 1971

The Reticular Formation and acetylcholine

Pontine Tegmentum stimulation induces:





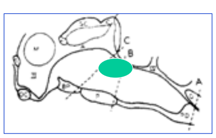
Ach release in cerebral cortex

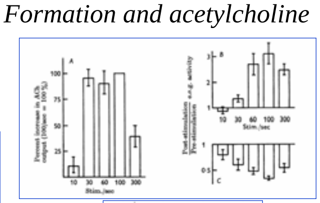
EEG activation

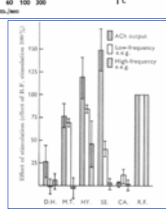
-Acetylcholine mediates EEG activation
- Acetylcholine comes from the pontine tegmentum

Kanai and Szerb, Nature 205: 80-82, 1965; Szerb, J Physiol 192: 329-343, 1967

The Reticular Formation and acetylcholine

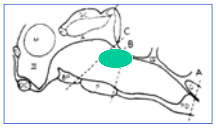


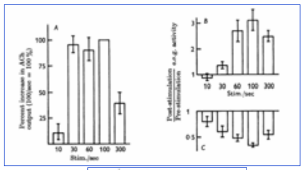


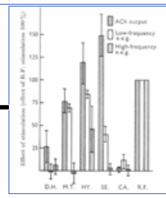


Szerb, J Physiol 192: 329-343, 1967

The Reticular Formation and acetylcholine



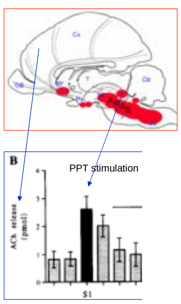




~~Sufficient?~~

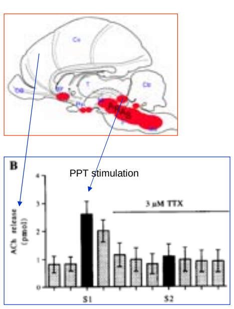
Szerb, J Physiol 192: 329-343, 1967

The Reticular Formation and acetylcholine



Rasmusson et al., Neuroscience 60: 665-677, 1994.

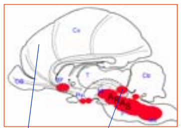
The Reticular Formation and acetylcholine



TTX or procaine
infused in the BF

Rasmusson et al., Neuroscience 60: 665-677, 1994.

The Reticular Formation and acetylcholine



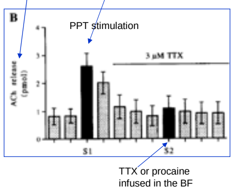


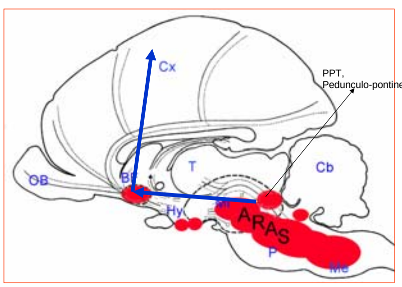
Table 2. E2/E1 ratio for evoked acetylcholine release and low-voltage fast activity

Drug	ACh release Mean	ACh release S.E.M.	ACh release n	LVFA Mean	LVFA S.E.M.	LVFA n
Control	1.016	0.112	5	0.946	0.099	4
Drug application through NBM probe:						
TTX 0.3 µM	0.538	0.135	5	0.380	0.380	2
TTX 1.0 µM	0.482	0.073	4	—	—	—
TTX 3.0 µM	0.149	0.042	7	0	0	4
Procaine 20%	0.233	0.022	6	—	—	—
Mg 10 mM/Ca 0	0.377	0.116	3	0.754	—	1
Co 10 mM/Ca 0	0.373	0.108	3	0.567	0.248	3
Co 20 mM/Ca 0	0.357	0.107	3	0.183	0.044	3
Kynurenate 0.25 mM	0.813	0.081	3	0.682	0.040	3
Kynurenate 1 mM	0.827	0.113	3	0.495	0.099	3
Kynurenate 5 mM	0.347	0.088	3	0.278	0.100	2
Kynurenate 10 mM	0.254	0.079	4	0.589	0.182	4
Scopolamine 0.1 µM	1.037	0.216	3	0.947	—	1
Scopolamine 10 µM	0.754	0.085	5	—	—	—
Scopolamine 30 µM	1.507	0.294	3	0.938	0.162	2
Mecamylamine 1 mM	0.805	0.070	3	0.745	0.164	2
Drug application through cortical probe:						
TTX 1 µM	0.009	0.011	3	0.339	0.177	3
Systemic (s.c.):						
Scopolamine 0.5 mg/kg	1.059	0.087	3	0	0	3

Conclusion 1:
ARAS does not mediate EEG activation (and Ach release in cx) via a cholinergic projection from the PPT (the projection is glutamatergic)

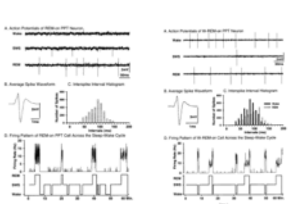
Rasmusson et al., Neuroscience 60: 665-677, 1994.

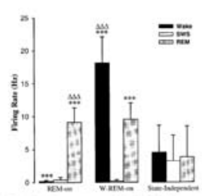
The Reticular Formation and acetylcholine



Lehmannn et al., Neuroscience 5:1161-1174, 1980; Haring and Wang, Brain Res 366: 152-158, 1986; Semba et al., J Comp Neurol 267: 433-453, 1988; Jones and Cuello, Neuroscience 31: 37-61, 1989 .

Firing of PPT neurons in sleep and waking





Datta and Siwek, J Neurosci Res 70: 611-621, 2002

The cholinergic basal forebrain and arousal

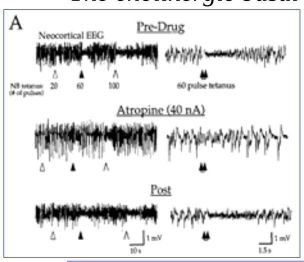
Supporting evidence:

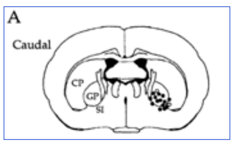
- excitotoxic lesions of the nucleus basalis of Meynert (NB) make the cortical EEG of awake animals resistant to activation

- NB stimulation results in cortical Ach release, EEG activation, and depolarization of cortical neurons

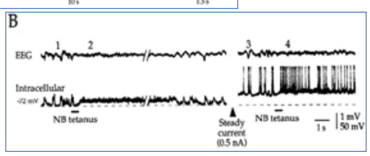
- NB neurons fire the most when the cortex is activated

The cholinergic basal forebrain and arousal





Metherate et al., J Neurosci 12: 4701-4711, 1992



The cholinergic basal forebrain and arousal

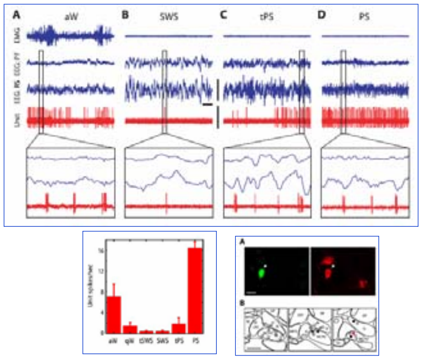
Supporting evidence:

- excitotoxic lesions of the nucleus basalis of Meynert (NB) or SI make the cortical EEG of awake animals resistant to desynchronization

- NB stimulation results in cortical Ach release, EEG activation, and depolarization of cortical neurons

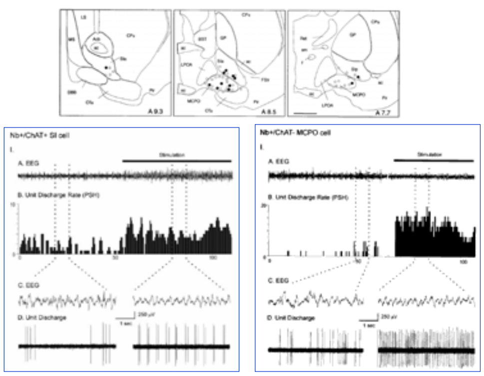
- NB neurons fire the most when the cortex is activated

The cholinergic basal forebrain and arousal



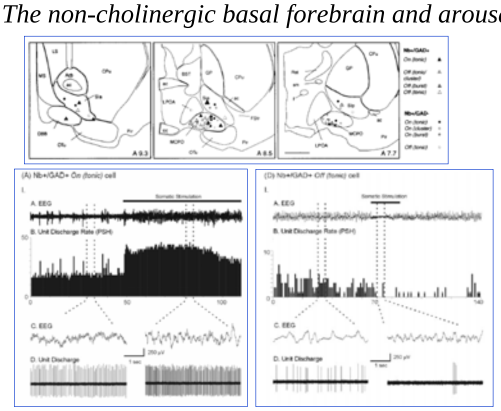
Lee et al., J Neurosci 25: 4365-4369, 2005

The cholinergic basal forebrain and arousal



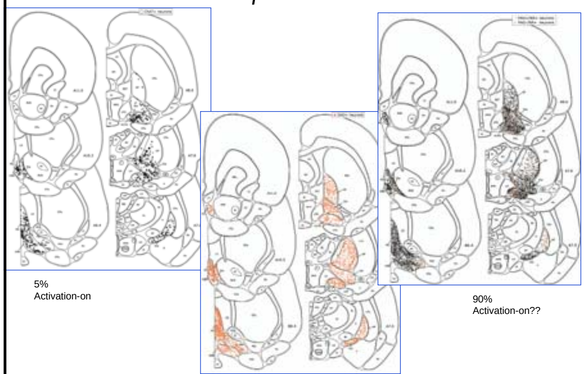
Manns et al. J Neurosci 20: 1505-1518, 2000

The non-cholinergic basal forebrain and arousal



Manns et al. J Neurosci 20: 9252-9263, 2000

The basal forebrain and arousal



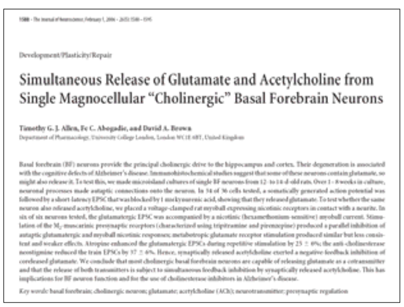
5%
Activation-on

90%
Activation-on??

33%
Activation-on or off

Gritti et al., Neuroscience 143: 1051-1064, 2006

Cholinergic/glutamatergic BF neurons



1588 • The Journal of Neuroscience, February 1, 2006 • 26(5):1588–1595

Development/Plasticity/Repair

Simultaneous Release of Glutamate and Acetylcholine from Single Magnocellular "Cholinergic" Basal Forebrain Neurons

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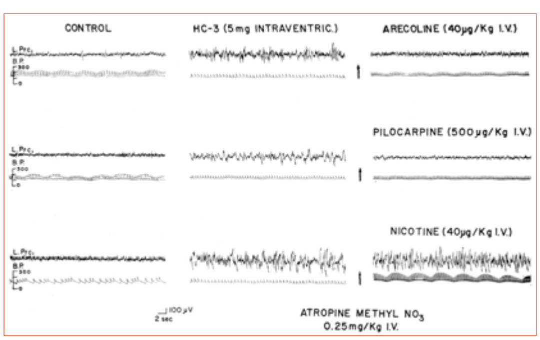
Department of Pharmacology, University College London, London WC1E 6BT, United Kingdom

Basal forebrain (BF) neurons provide the principal cholinergic drive to the hippocampus and cortex. Their degeneration is associated with the cognitive defects of Alzheimer's disease. Immunohistochemical studies suggest that some of these neurons contain glutamate, so might also release it. To test this, we made microisland cultures of single BF neurons from 12- to 14-d-old rats. Over 1–8 weeks in culture, neuronal processes made autaptic connections onto the neuron. In 34 of 36 cells tested, a somatically generated action potential was followed by a short-latency EPSC that was blocked by 1 mM kynurenic acid, showing that they released glutamate. To test whether the same neuron also released acetylcholine, we placed a voltage-clamped rat myoball expressing nicotinic receptors in contact with a neurite. In six of six neurons tested, the glutamatergic EPSC was accompanied by a nicotinic (hexamethonium-sensitive) myoball current. Stimulation of the M_2-muscarinic presynaptic receptors (characterized using tripitramine and pirenzepine) produced a parallel inhibition of autaptic glutamatergic and myoball nicotinic responses; metabotropic glutamate receptor stimulation produced similar but less consistent and weaker effects. Atropine enhanced the glutamatergic EPSCs during repetitive stimulation by 25 ± 6%; the anti-cholinesterase neostigmine reduced the train EPSCs by 37 ± 6%. Hence, synaptically released acetylcholine exerted a negative feedback inhibition of coreleased glutamate. We conclude that most cholinergic basal forebrain neurons are capable of releasing glutamate as a cotransmitter and that the release of both transmitters is subject to simultaneous feedback inhibition by synaptically released acetylcholine. This has implications for BF neuron function and for the use of cholinesterase inhibitors in Alzheimer's disease.

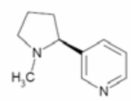
Key words: basal forebrain; cholinergic neuron; glutamate; acetylcholine (ACh); neurotransmitter; presynaptic regulation

Ach activating effect is mainly muscarinic



Domino et al. Role of cholinergic mechanisms in states of wakefulness and sleep. Progress in Brain Res 28: 113-133, 1968.

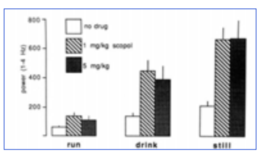
Mechanisms of nicotine-induced waking



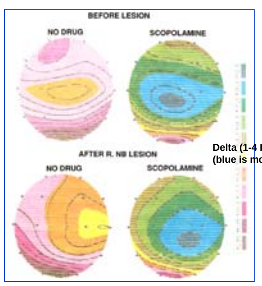
(*S*)-nicotine **10**

- Release of glutamate from thalamo-cortical axons
- Release of Ach from cholinergic axons (e.g. from BF neurons)
- Release of NA from LC neurons
- Inhibition of VLPO neurons (via NA)

Scopolamine effects on the EEG



The effect of scopolamine on the EEG is much greater during quiet than during active waking

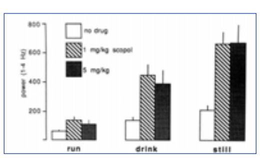


Delta (1-4 Hz) power (blue is more)

Scopolamine given after right lesion of the BF increases slow waves on both sides (i.e. the cholinergic lesion was not complete)

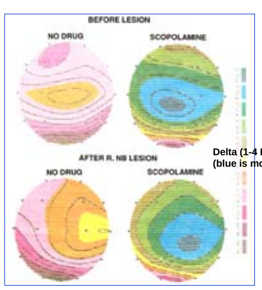
Buzsaki et al. J Neurosci 8: 4007-4026, 1988

Scopolamine effects on the EEG



The effect of scopolamine on the EEG is much greater during quiet than during active waking

~~Necessary~~ ?



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Summary of acetylcholine and waking

- Ach is important, but neither necessary nor sufficient for waking/EEG activation

- cholinergic basal forebrain plays a major role

- Ach acts mainly, but not only through muscarinic receptors