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GABA in locus coeruleus in REMS regulation

Presentation for
J. Sleep Dis. Therapy

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SLEEP AND WAKING ARE INSTINCT BEHAVIORS AND THEY REPRESENT STATES OF CONSCIOUSNESS

SLEEP IS A REVERSIBLE STATE WHERE CONSCIOUSNESS REMAINS IN A SUBDUED STATE

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BASED ON EEG AND EMG SLEEP-WAKING WAS OBJECTIVELY CLASSIFIED INTO AWAKE AND SLEEP

ADDITIONAL PARAMETER, CLASSICALLY AT LEAST EOG, HELPED IDENTIFICATION OF REM SLEEP (REMS)

(PGO AND HIPPOCAMPAL WAVES ALSO HAVE BEEN USED)

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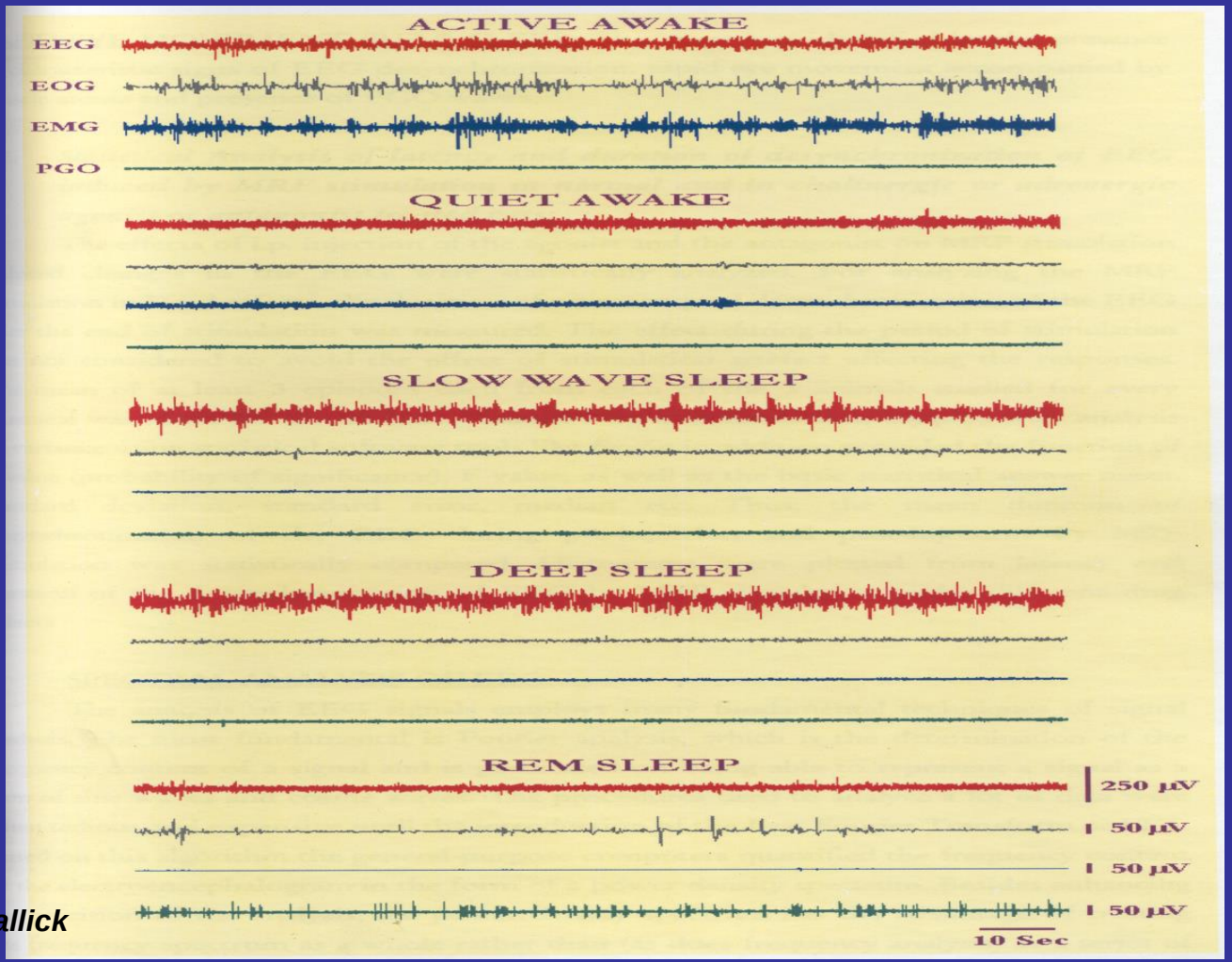
ISSN: 2167-0277

SLEEP-WAKING STAGES IN CAT



Thankachan & Mallick

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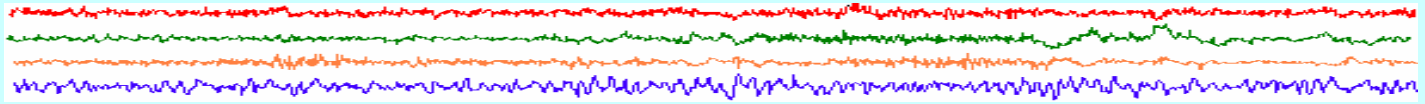
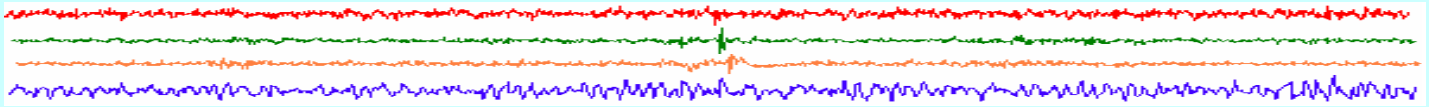
SLEEP-WAKING STAGES IN RAT

EEG
EOG
EMG
Hipp

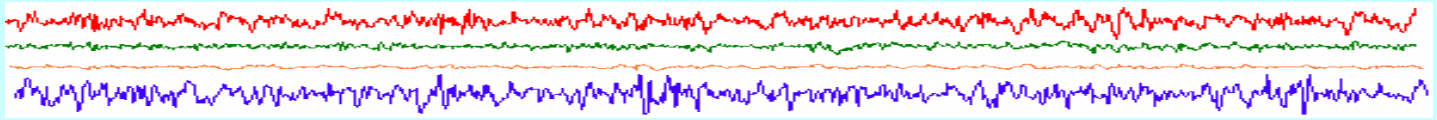
Active Wakefulness



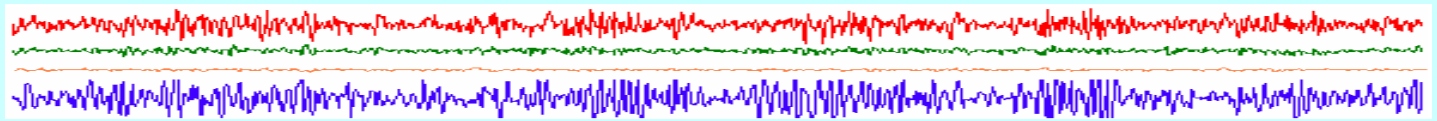
Quiet Wakefulness



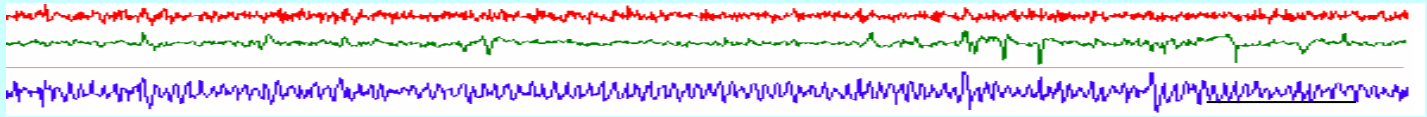
Slow Wave Sleep 1



Slow Wave Sleep 2



REM Sleep



100µV
25µV
50µV
50µV

4 Sec

Kaur & Mallick

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HOW IS REM SLEEP (REMS) REGULATED BY THE BRAIN?

(Neural Regulation of REMS)

Depending on the firing rate of neurons during REMS, in the brain there are

- ***REM-ON neurons (those increasing firing)***

and

- ***REM-OFF neurons (those decreasing firing/silent)***

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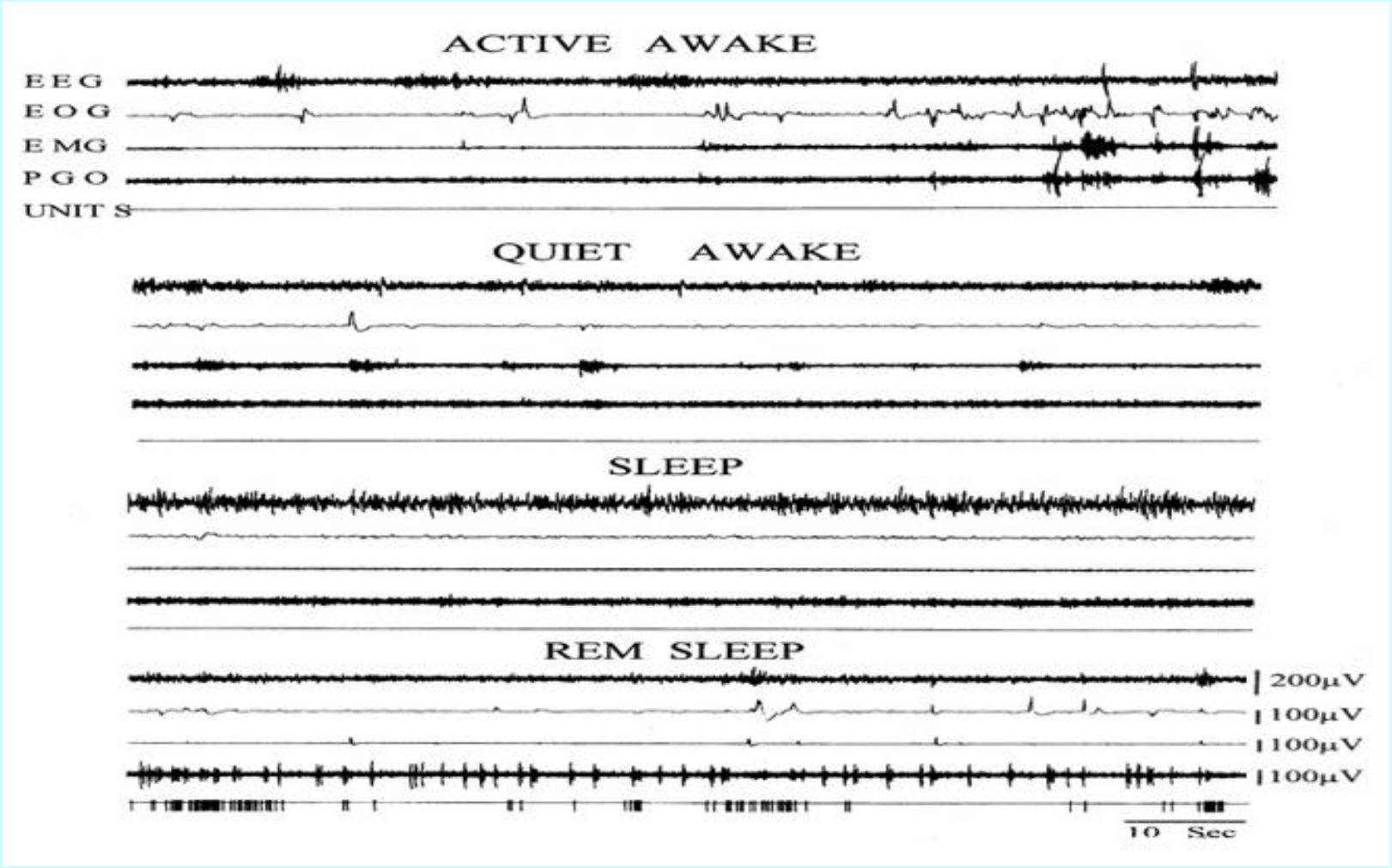
REM-ON NEURON



Mallick et al., Sleep Res. Online, 1998

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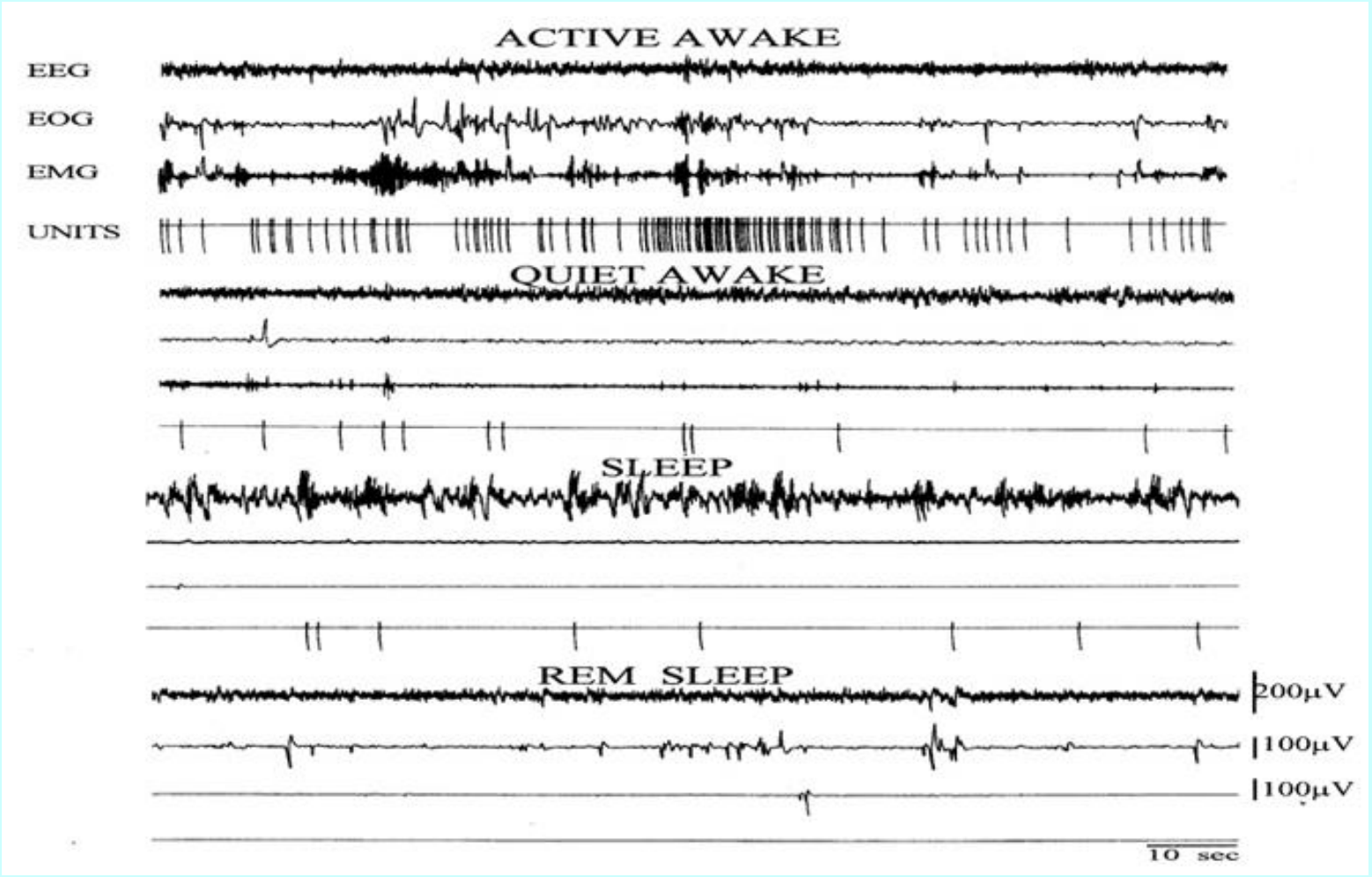
REM-OFF NEURON



Mallick et al., Sleep Res. Online, 1998

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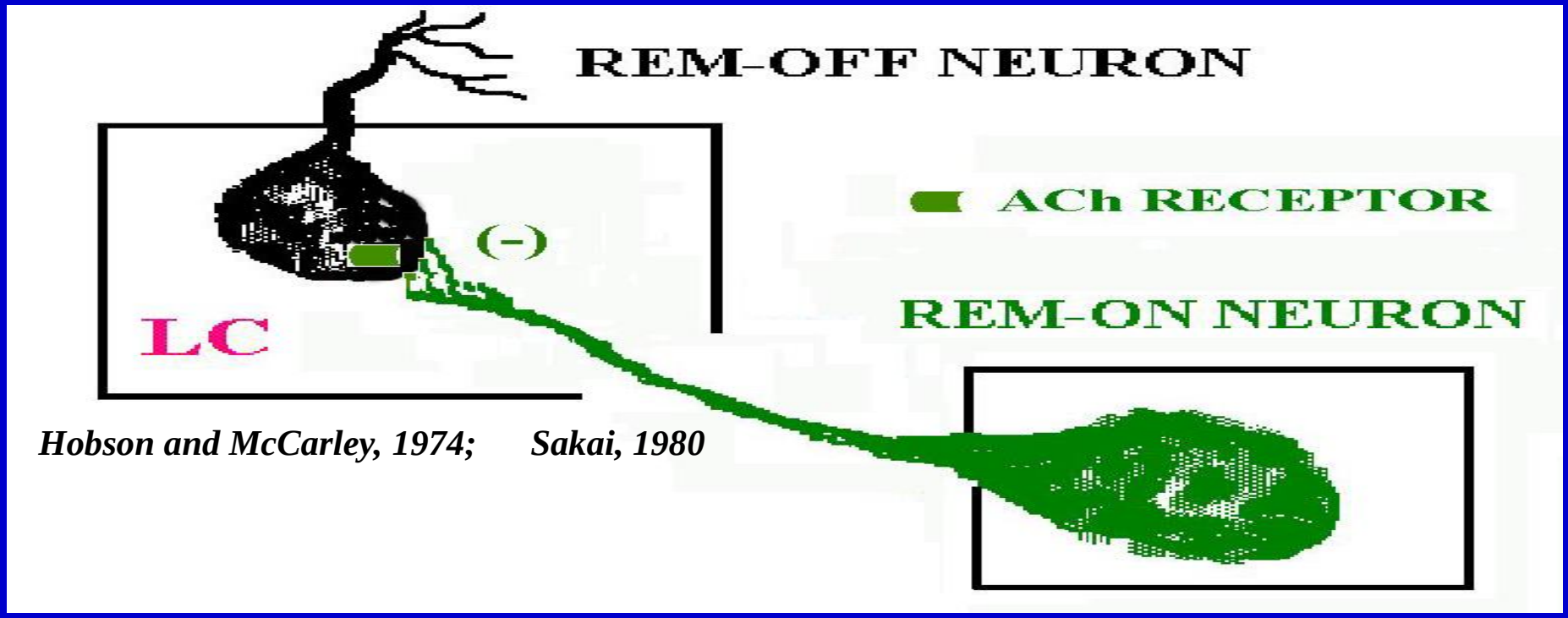

Hobson and McCarley, 1974; *Sakai, 1980*

Based on recording of REM-ON and REM-OFF neuronal activities from isolated, independent studies it was proposed that for REMS

i) activity of REM-ON neurons inhibit REM-OFF neurons;

ii) acetylcholine from REM-ON neurons inhibit the Noradrenergic (NA-ergic) REM-OFF neurons

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QUESTIONS WE RAISED/ASKED

- **Is cessation of NA-ergic REM-OFF neuronal activities in locus coeruleus (LC) a pre-requisite/pre-condition for REMS generation or it is an associated phenomenon**

- **Activation of REM-OFF neurons in LC should not allow REMS to happen**

- **Does acetylcholine inhibit the REM-OFF neurons**

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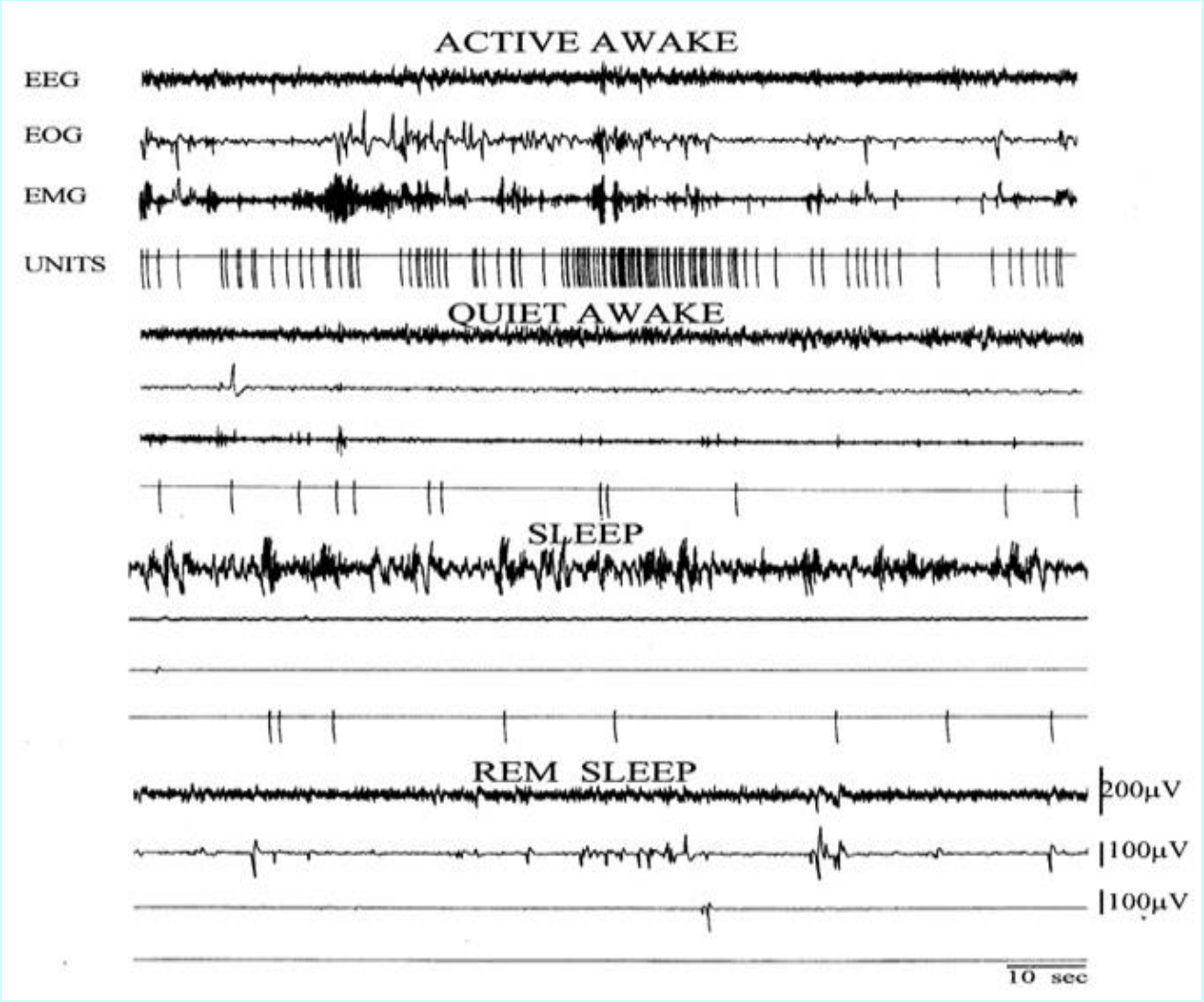
REM-OFF NEURON



HYPOTHESIS

Singh & Mallick, Neurosci. Res., 1996

IF LC REM-OFF NEURONS MUST STOP FIRING FOR GENERATION OF REMS

THEIR ACTIVATION IN AN ATTEMPT NOT TO ALLOW THEM TO CEASE FIRING

WOULD CAUSE REMS LOSS OR AT LEAST WOULD SIGNIFICANTLY REDUCE REMS

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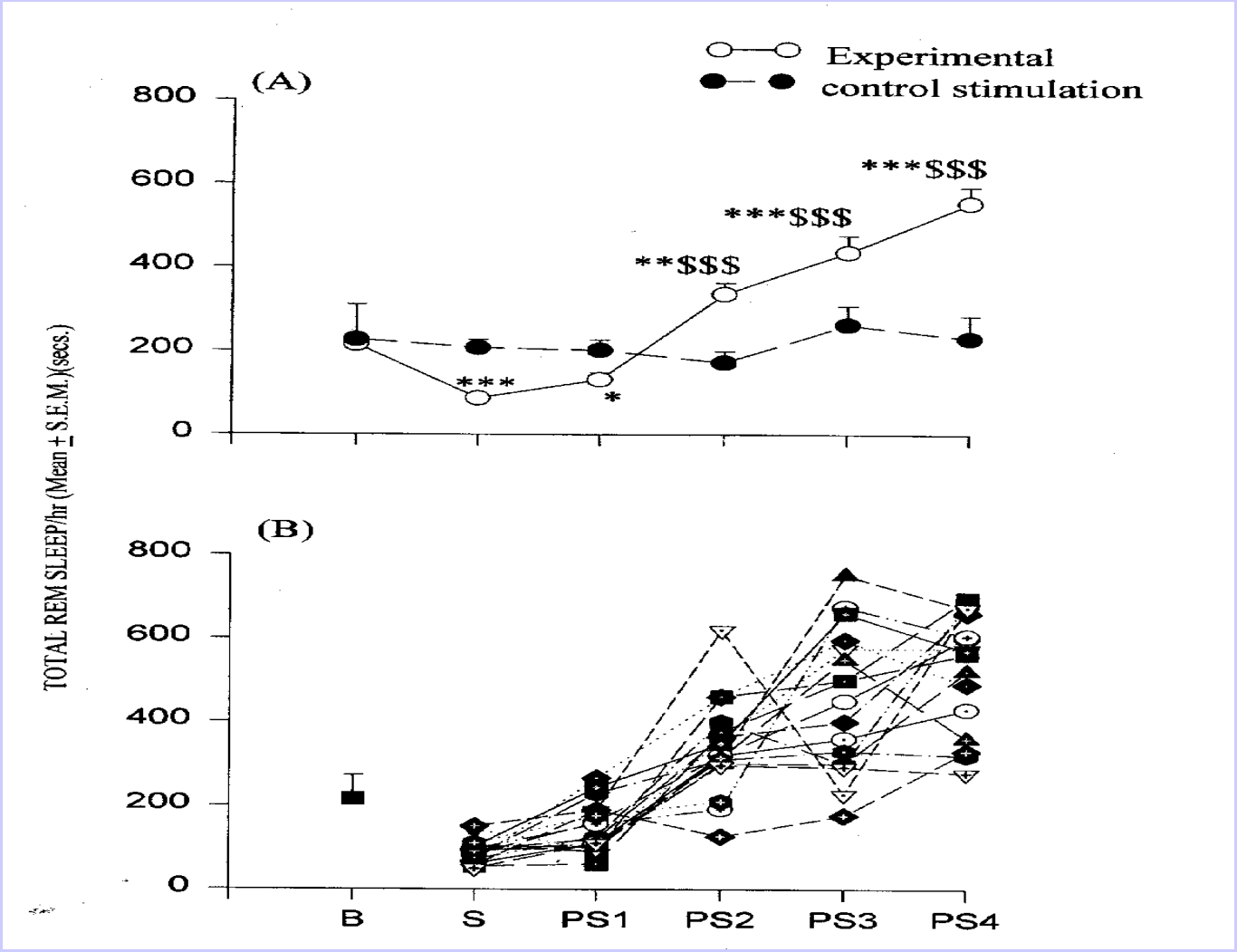
Mild sustained stimulation of LC reduced REMS



Cessation of activities of LC-NA-ergic REM-OFF neurons is a pre-requisite for the generation of REMS

Singh and Mallick, Neurosci. Res., 1996

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Previously, activities of REM-ON and REM-OFF neurons were recorded independently in separate animals, in isolated experiments on different days.

For confirmation and to understand their temporal correlation, we recorded in freely moving normally behaving, surgically prepared chronic animals, both REM-OFF and REM-ON neuronal activities simultaneously along with electrophysiological (EEG, EMG, EOG, PGO) waking-sleep-REMS patterns

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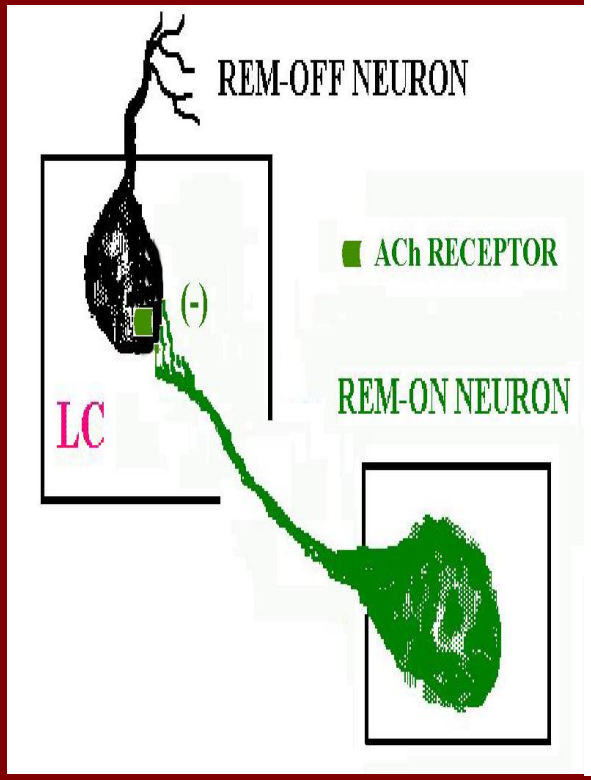
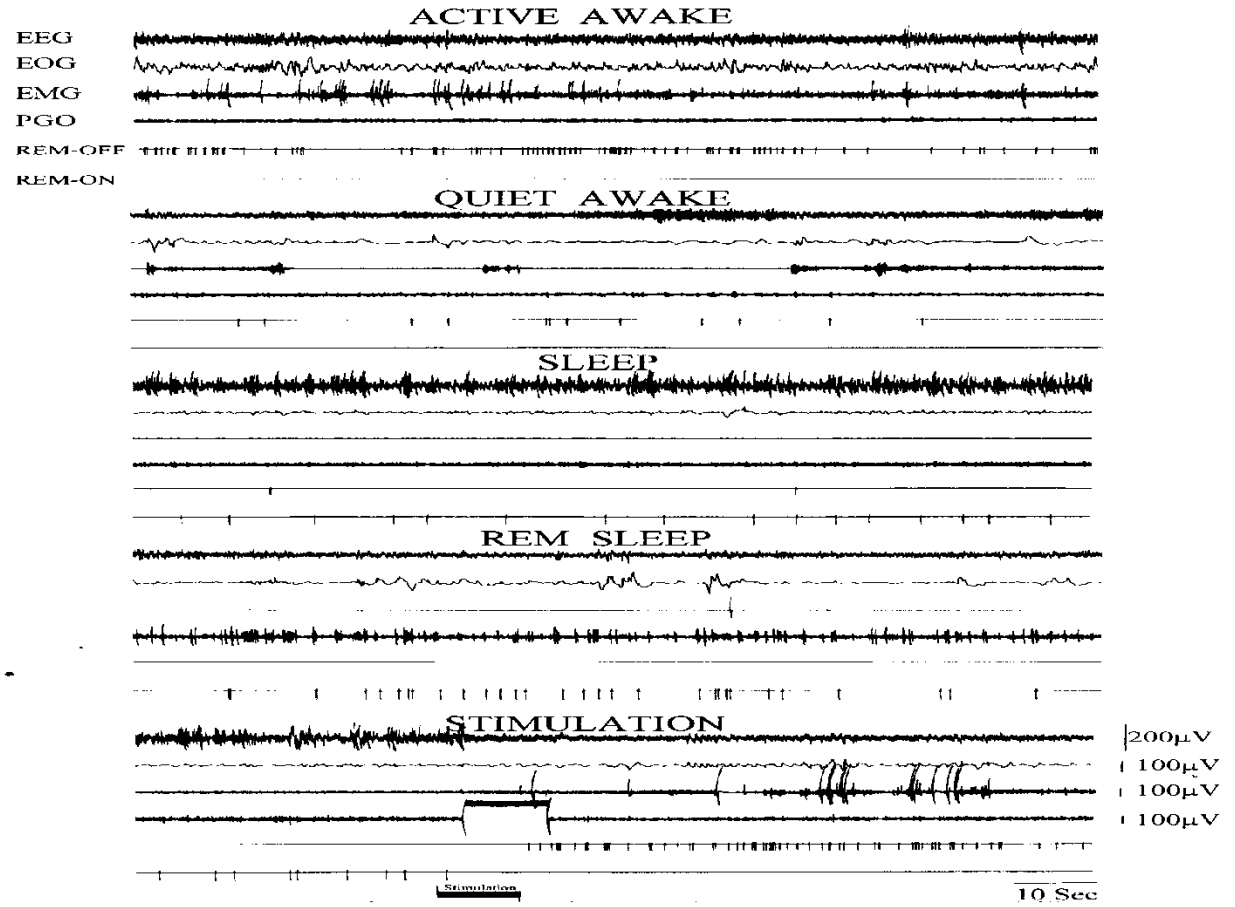
SIMULTANEOUS RECORDING OF REM-OFF AND REM-ON NEURONS





Mallick et al., Sleep Res. Online, 1998

Temporal correlation between REM-ON and REM-OFF neuronal

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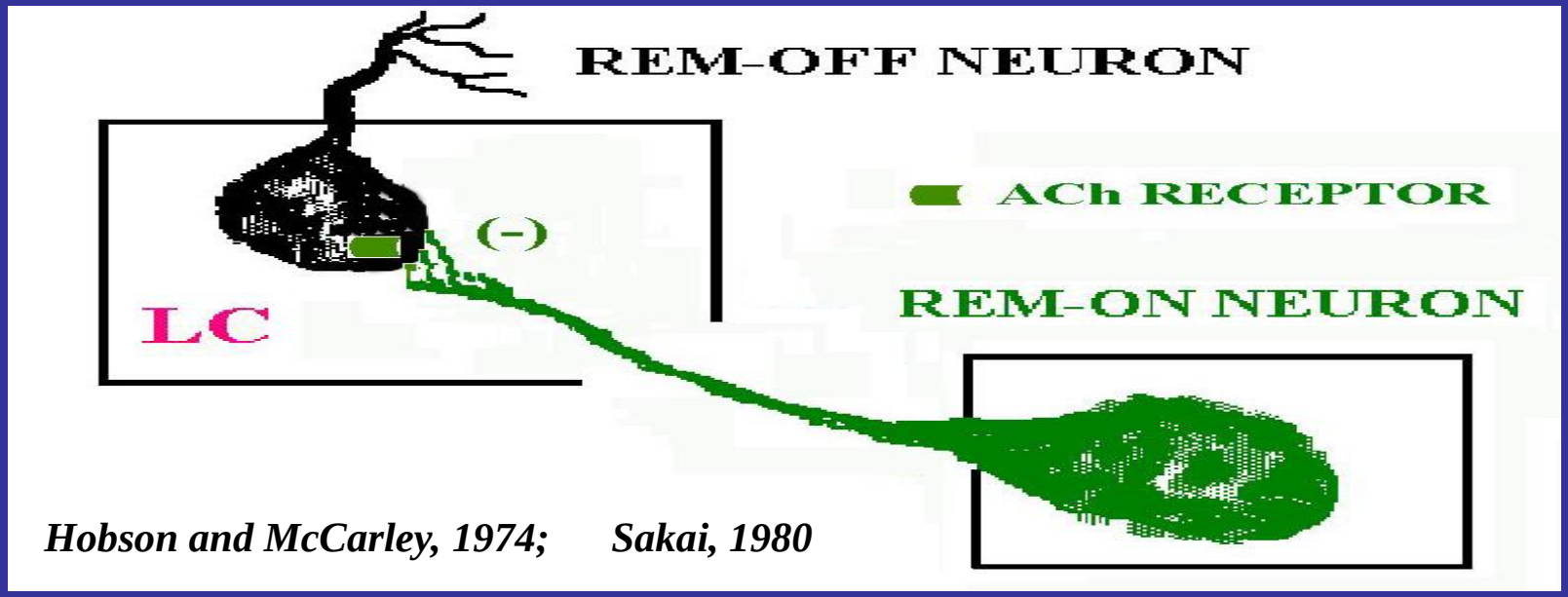

Hobson and McCarley, 1974; *Sakai, 1980*

REM-OFF NEURONS MUST STOP FIRING FOR REMS GENERATION

BUT HOW ?

***in vitro* studies showed that**
Acetylcholine depolarized LC neurons
i.e. not inhibition (*Egan and North, 1985*)

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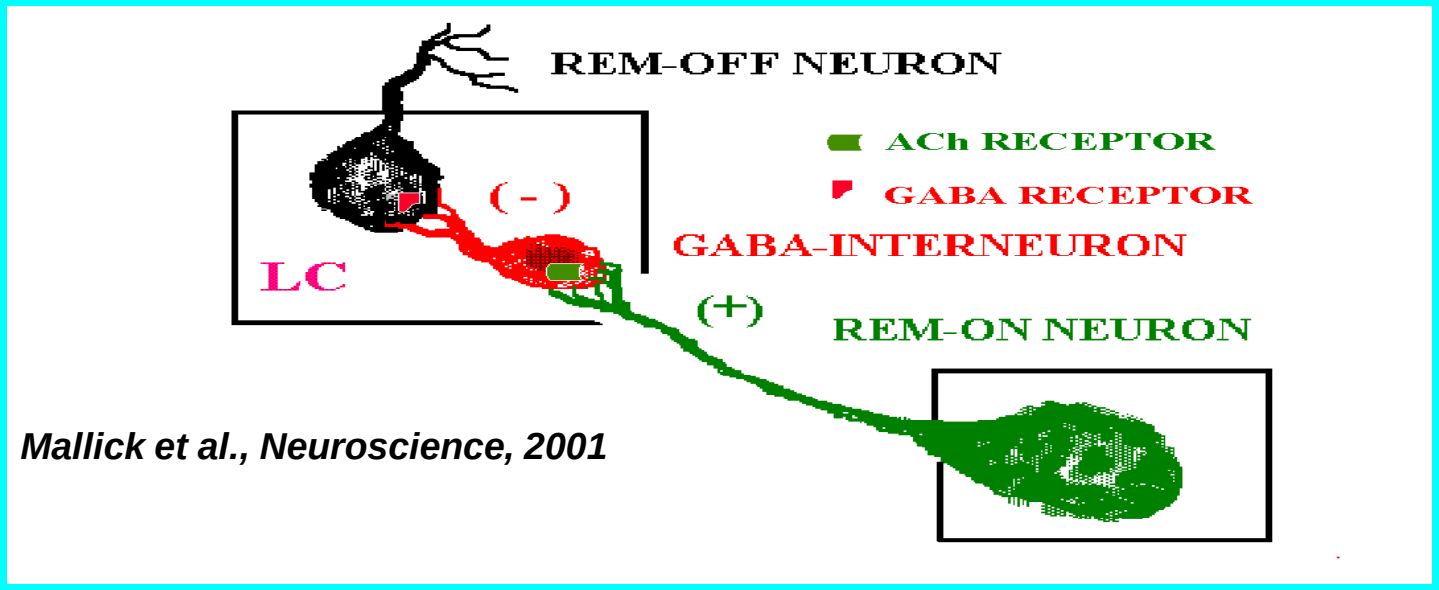
Therefore, it was hypothesized

In LC, excitatory cholinergic input from REM-ON neurons was translated into an inhibition on REM-OFF neurons through GABA interneuron for REMS generation



Mallick et al., Neuroscience, 2001

Challenge was to simultaneously gather information on Neuro-Micro-Anatomo-Pharmaco-Physiologico-Behavioral aspects

It was overcome by microinjection of agonist/antagonist of one or more types of receptors in LC in various sequence/combination

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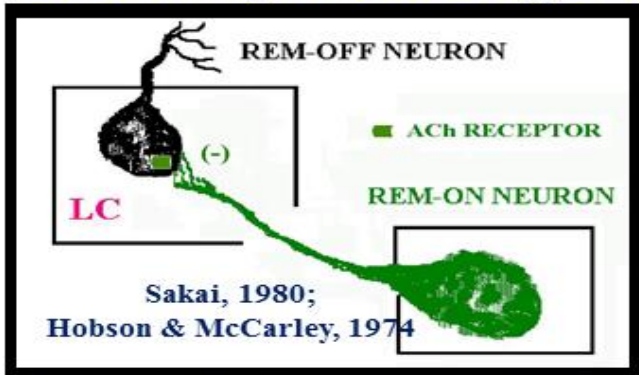
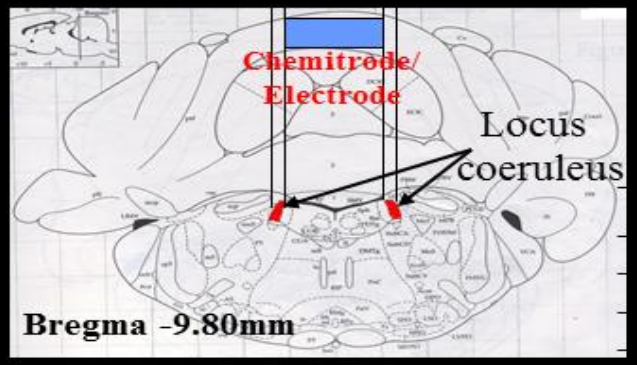
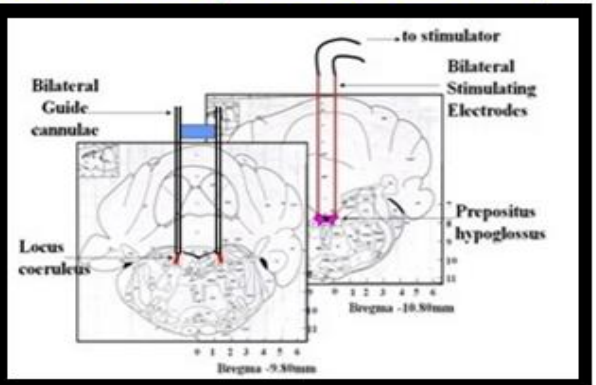
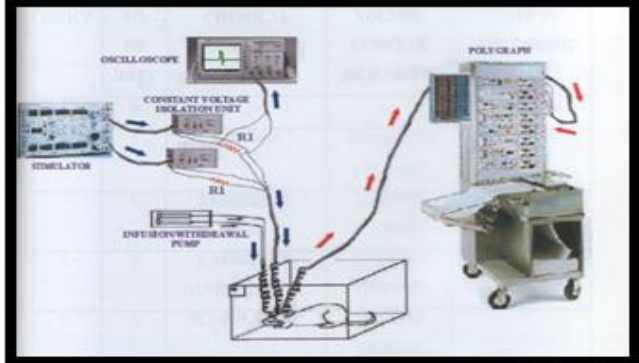
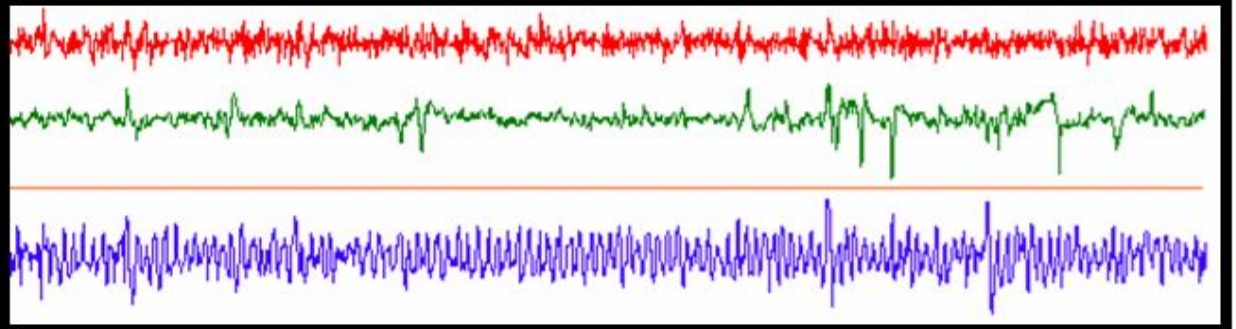
Recording in behaving rats by modulating LC neurons electrically or chemically











Following methods used/studies were carried out

- *Bilateral Chemitrode/Electrode implantation by Stereotaxic surgery*
- *<u>in vivo</u> studies in freely behaving surgically prepared chronic rats*
- *Stimulation of LC neurons*
- *Single or combination of agonist and/or antagonist microinjection into LC with/ without simultaneous stimulation of PrH*

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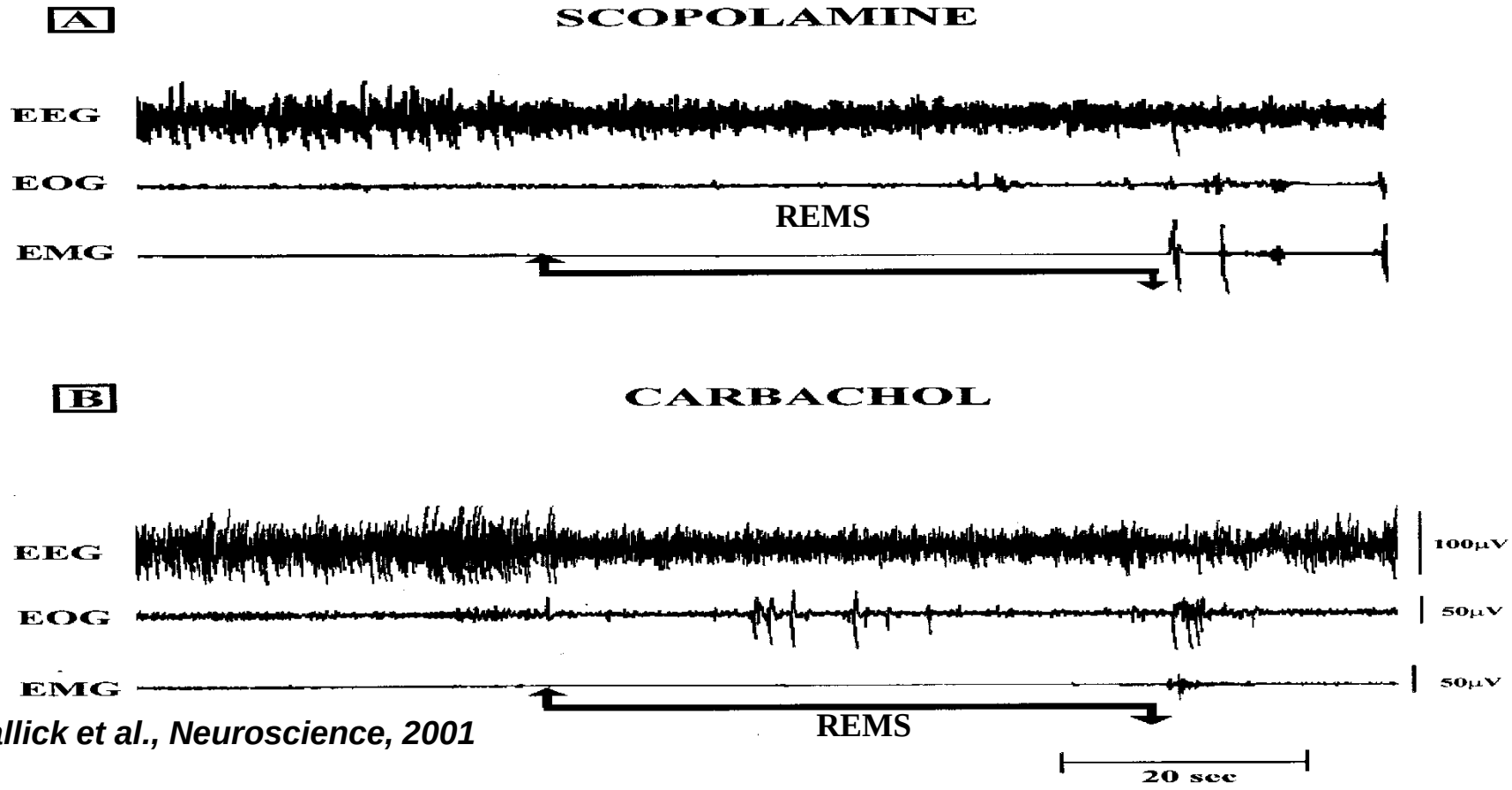
Effect of local microinjection of cholinergic antagonist (scopoloamine) and agonist (carbachol) bilaterally into the LC on REMS



Mallick et al., Neuroscience, 2001

REMS duration per episode was not affected, however, frequency of REMS generation was increased

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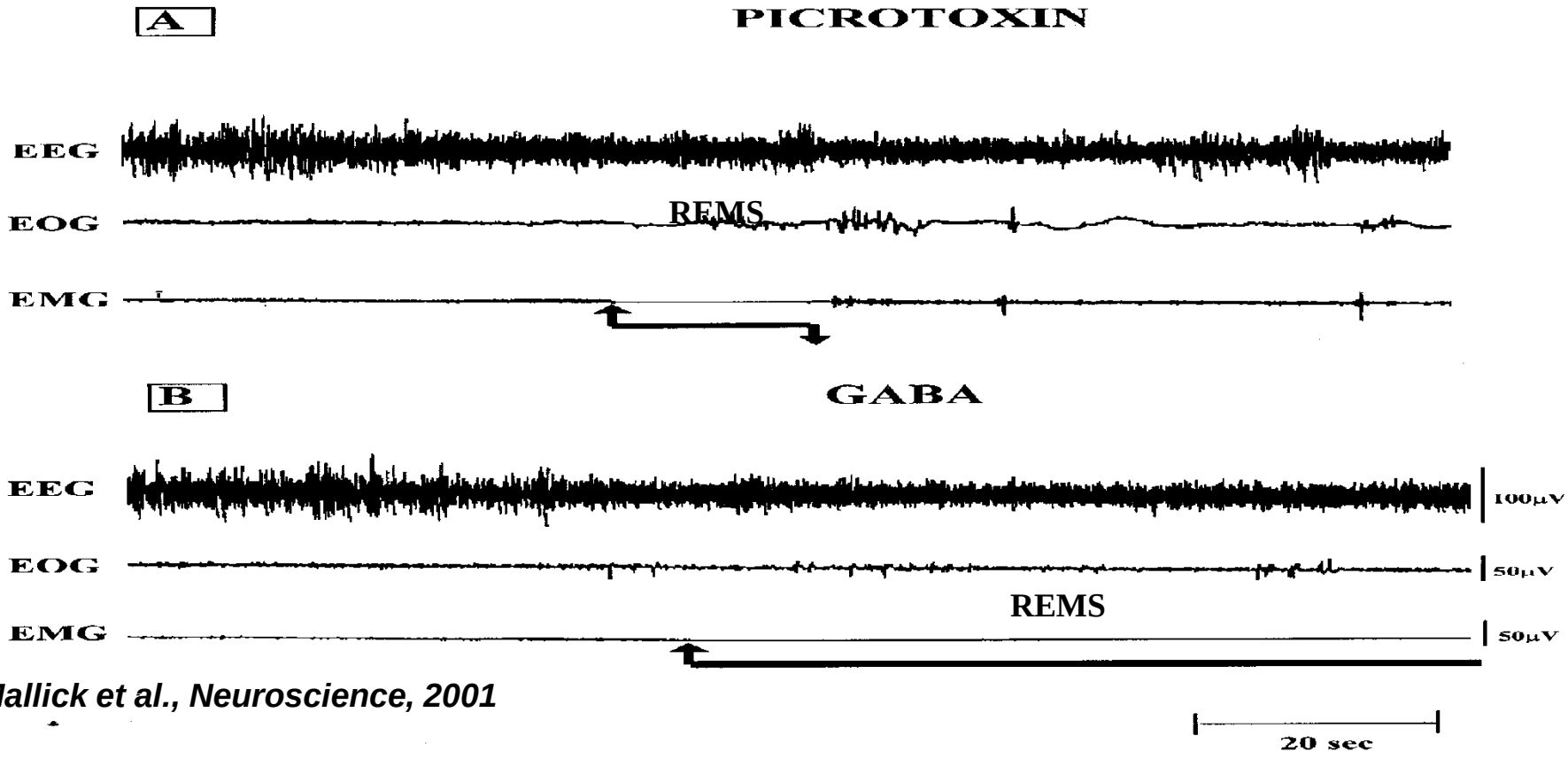
Effect of local microinjection of GABA-ergic antagonist (picrotoxin) and GABA bilaterally into the LC on REMS



Mallick et al., Neuroscience, 2001

REMS duration per episode was significantly affected, however, frequency of REMS generation remained unaffected

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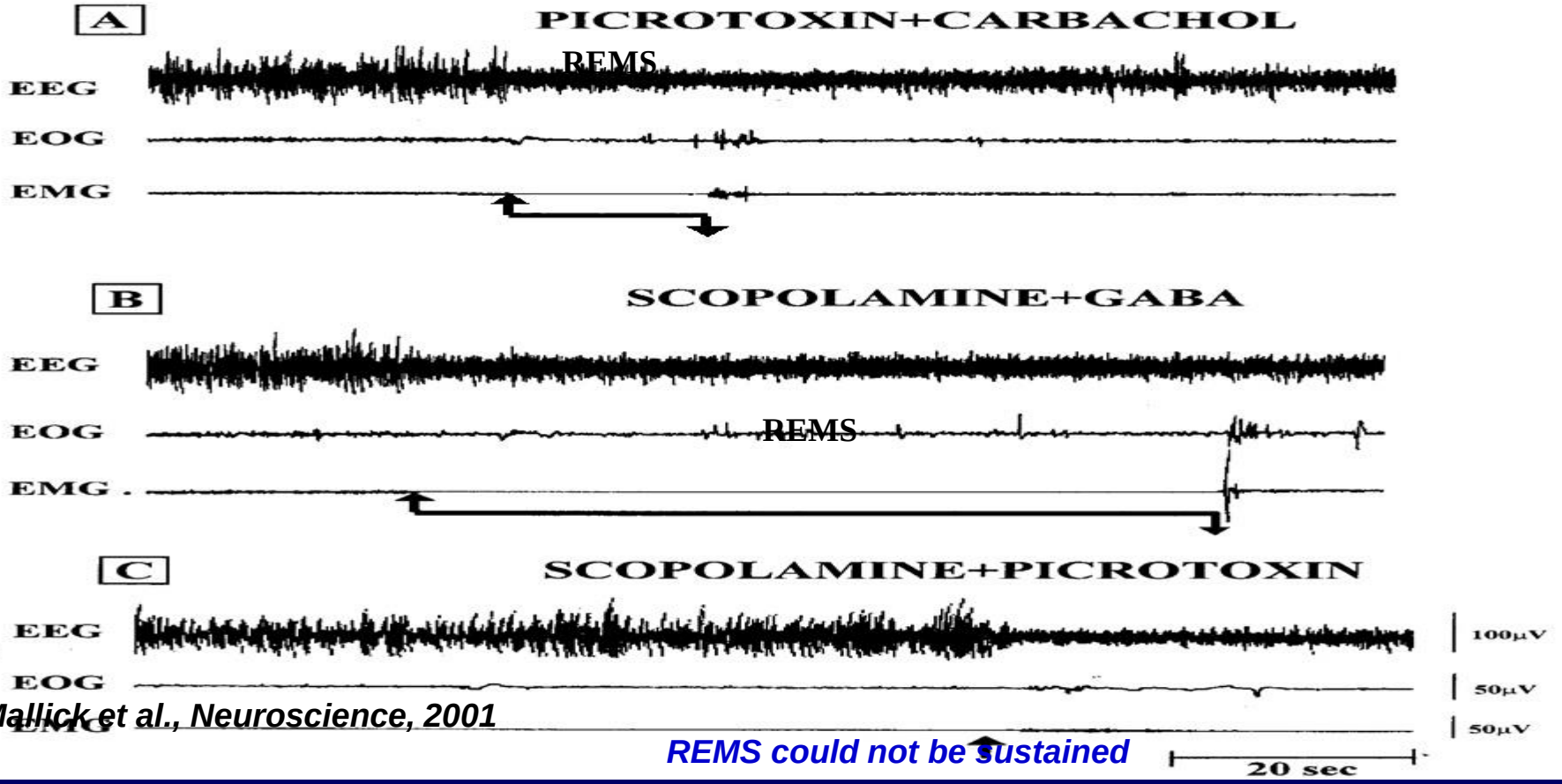
Effect of local microinjection of cholinergic and GABA-ergic antagonist/agonist in various combinations/sequences into the LC on REMS



Mallick et al., Neuroscience, 2001

REMS duration per episode was reduced in (A); it was increased in (B), while in (C) REMS did not continue

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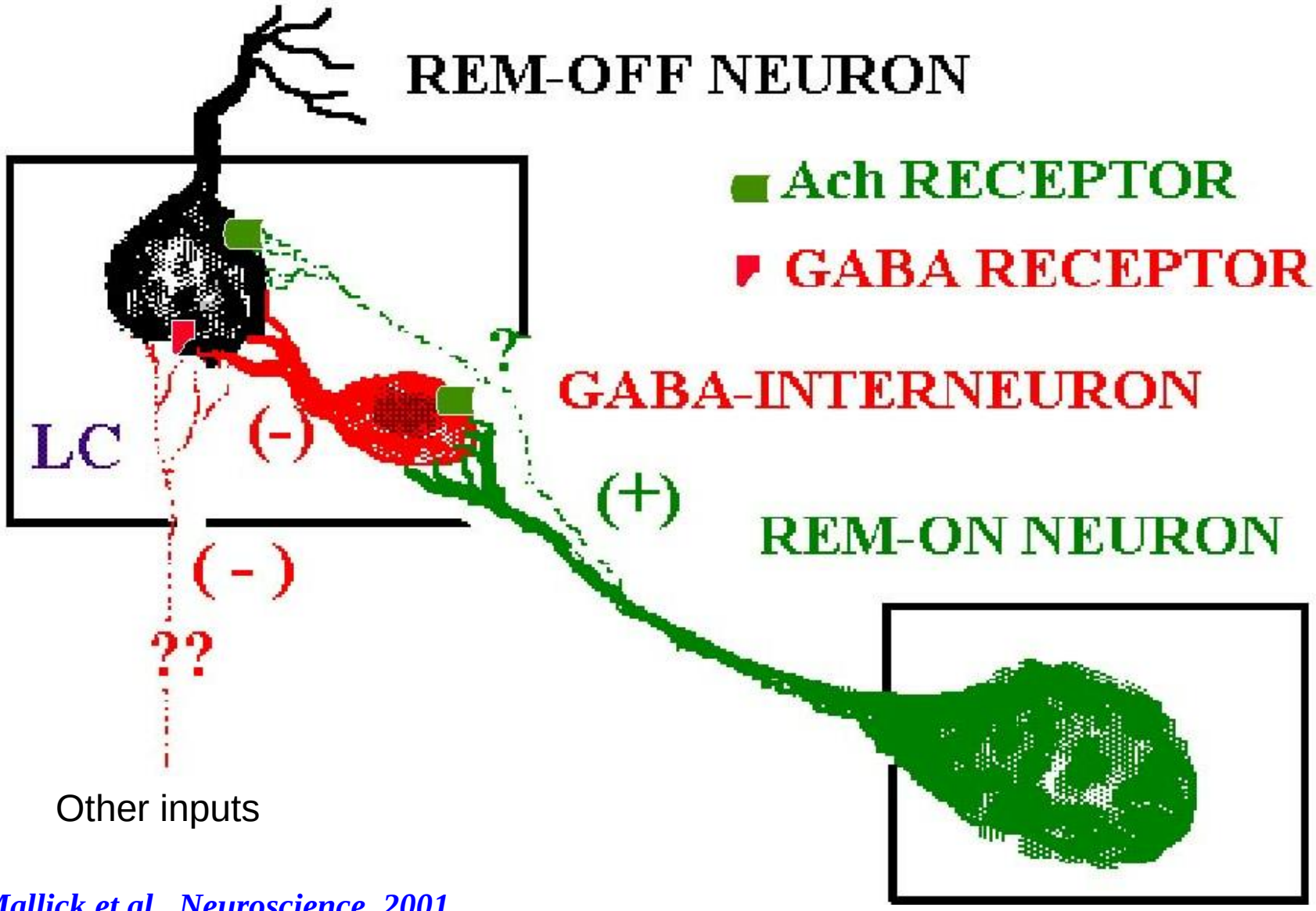

Mallick et al., Neuroscience, 2001

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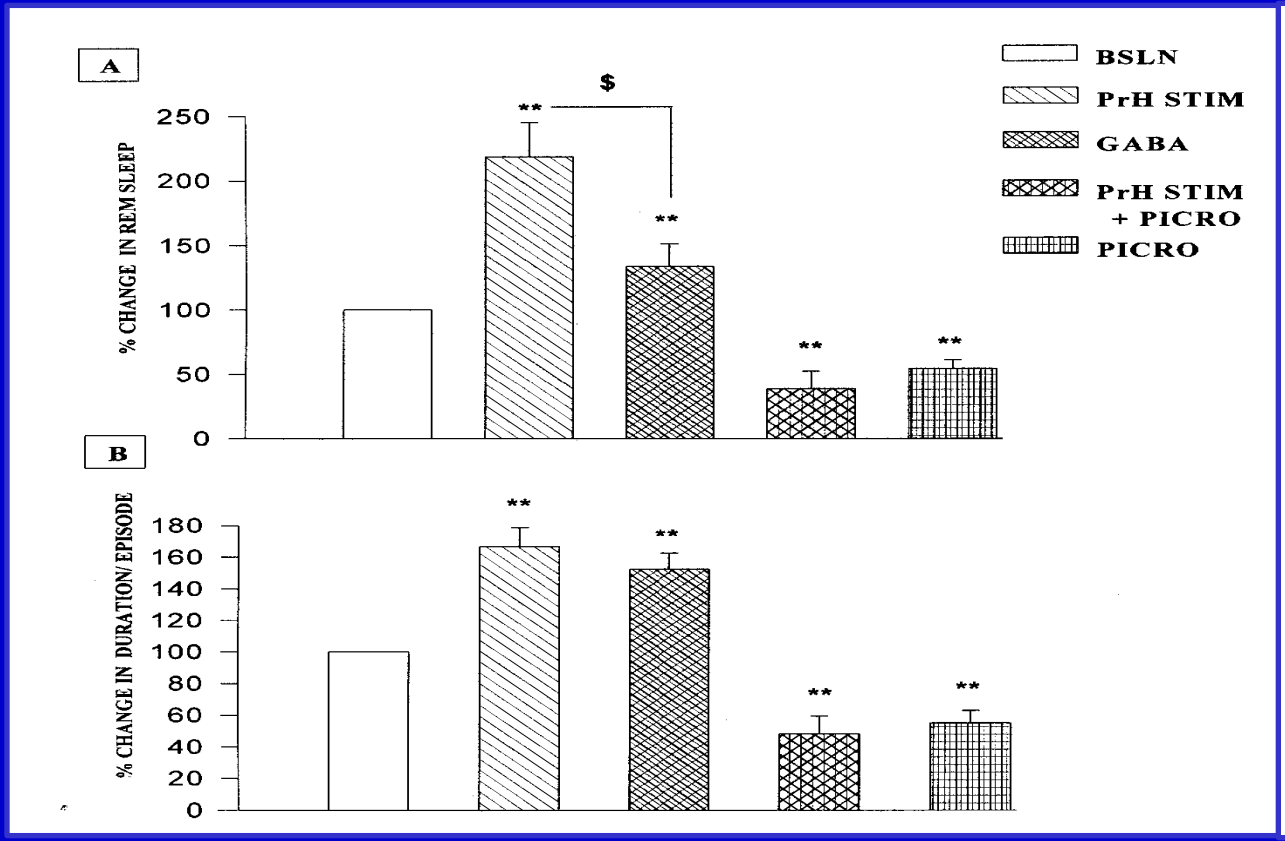
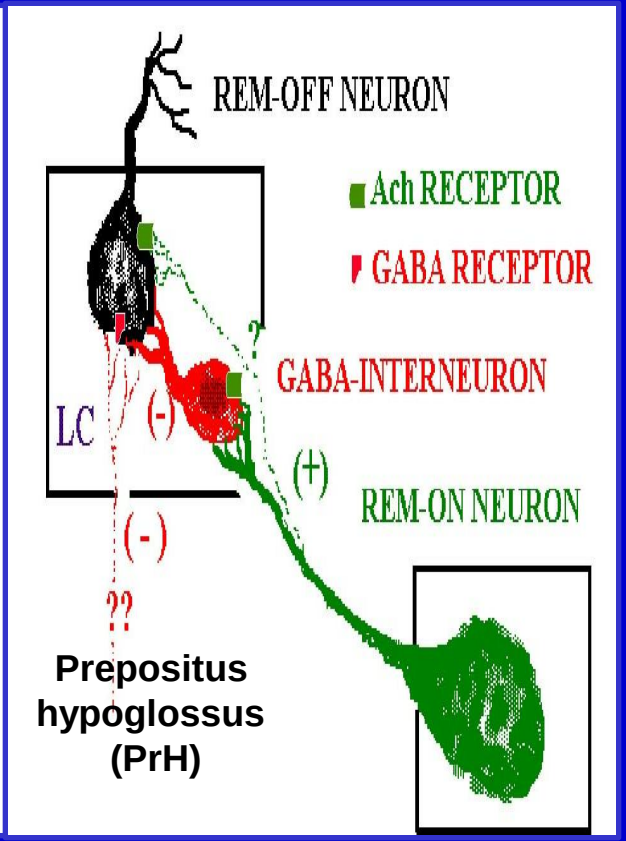
Comparison of the effect PrH Stimulation and microinjection of GABA and Picrotoxin in LC on REM Sleep





Kaur et al., Synapse, 2001

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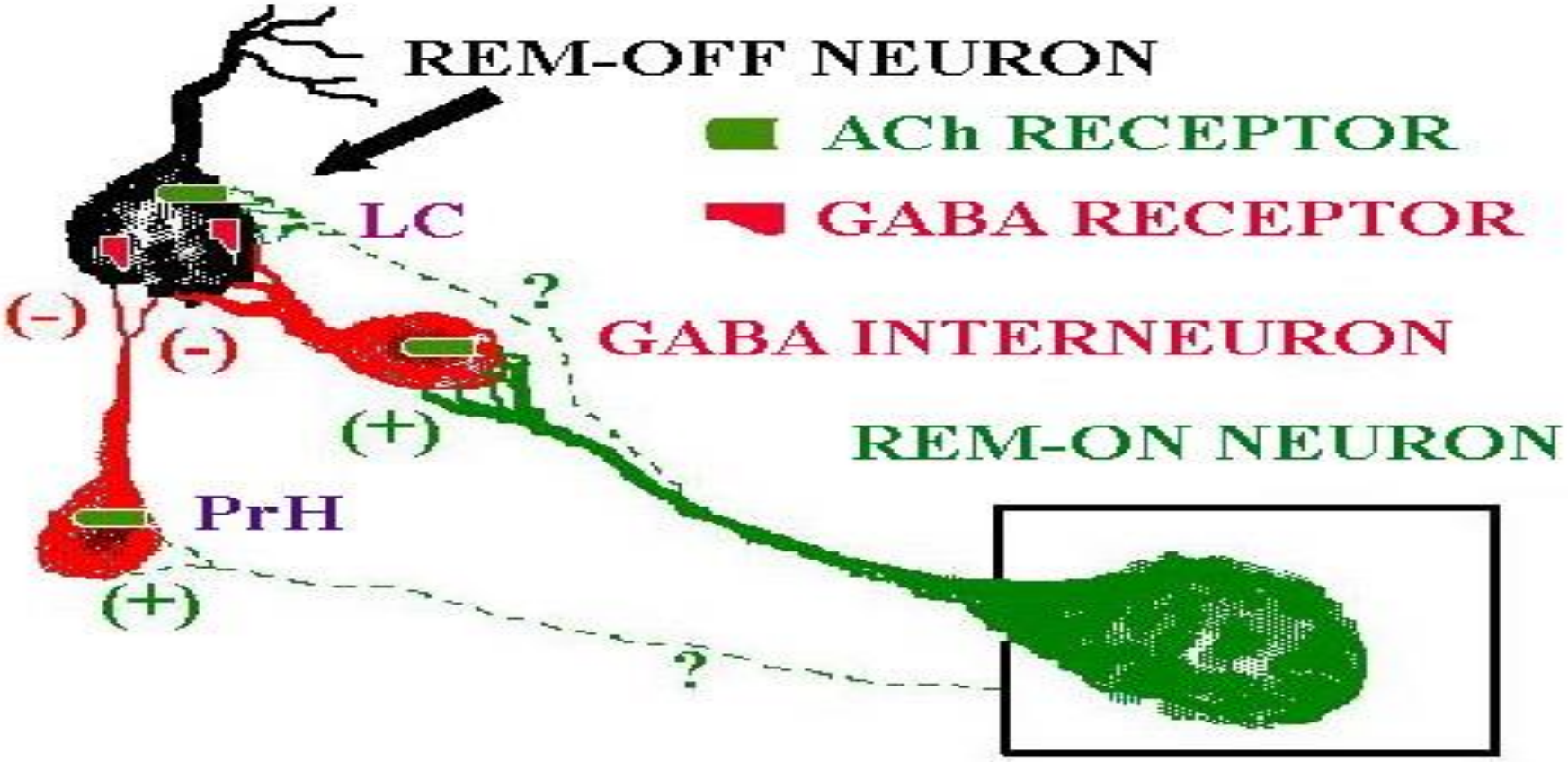
Mallick et al., Neuroscience, 2001 ; and Kaur et al., Synapse, 2001



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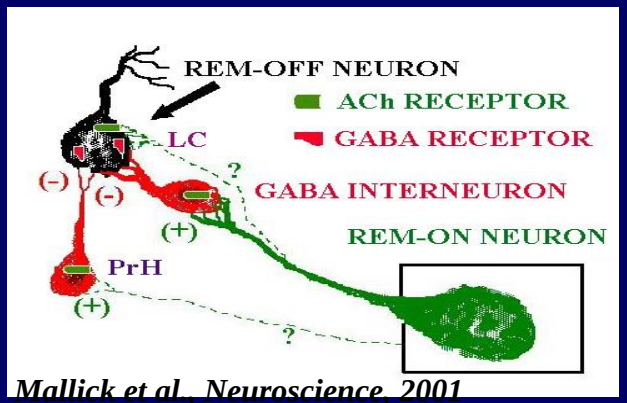
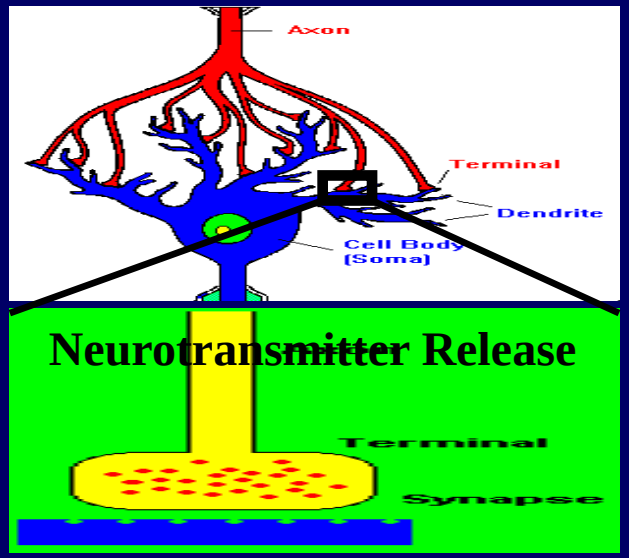
PHYSIOLOGICAL VALIDITY?



Mallick et al., Neuroscience, 2001



HYPOTHESIS

IF THE PROPOSED NEURAL CONNECTIONS ARE EXPERIMENTALLY DISTURBED SO THAT THE NA-ergic LC-REM-OFF NEURONS REMAIN ACTIVE,

REMS SHOULD BE SIGNIFICANTLY REDUCED

AND SIMULTANEOUSLY

REMS LOSS ASSOCIATED SYMPTOMS SHOULD BE EXPRESSED/OBSERVED DUE TO ELEVATED LEVELS OF NA EVEN IN NORMAL ANIMALS (Contd…)

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PHYSIOLOGICAL VALIDITY?

HYPOTHESIS

We had already shown that REMSD increased Na-K ATPase activity and it was due to elevated level of noradrenalin (NA) in the brain

(*Gulyani & Mallick, Neuroscience, 1995; Mallick et al., J. Neurochem., 2000*).

Therefore, we proposed that

i) GABA-antagonist, picrotoxin, into LC should not allow REM-OFF neurons to cease activity resulting in increased Na-K ATPase activity;

ii) Modulation of Na-K ATPase activity in LC should alter REM-OFF neuronal activity and REMS

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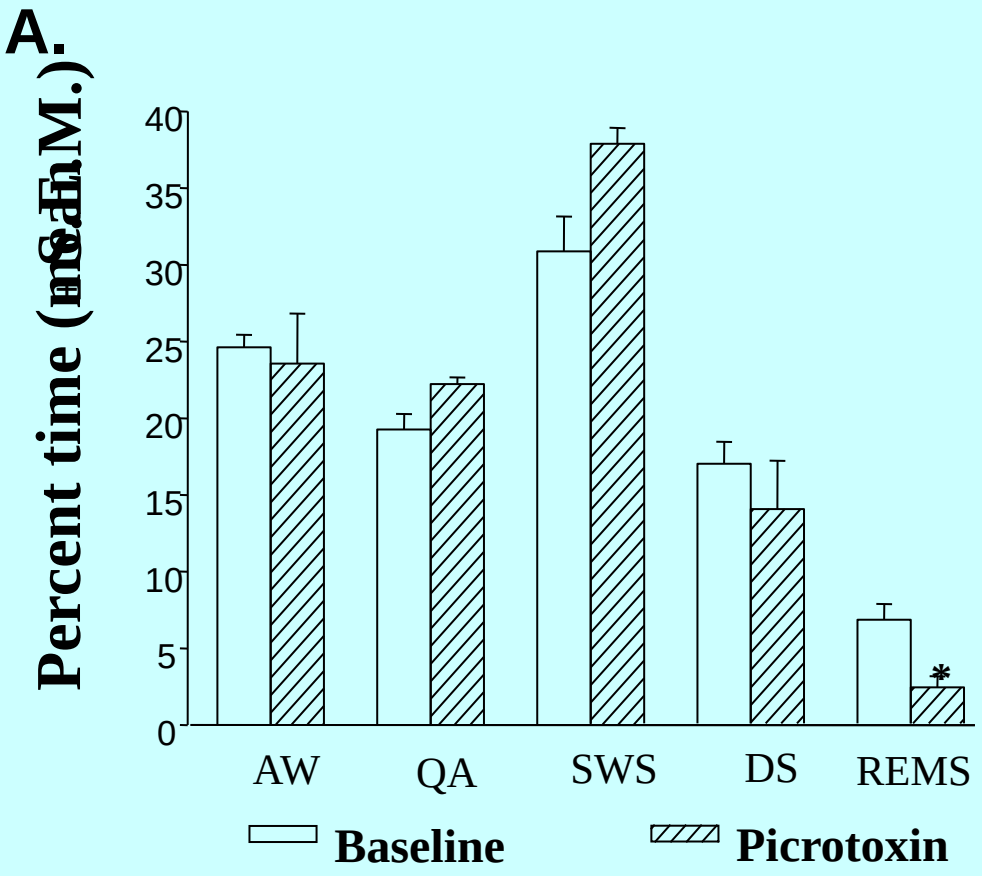
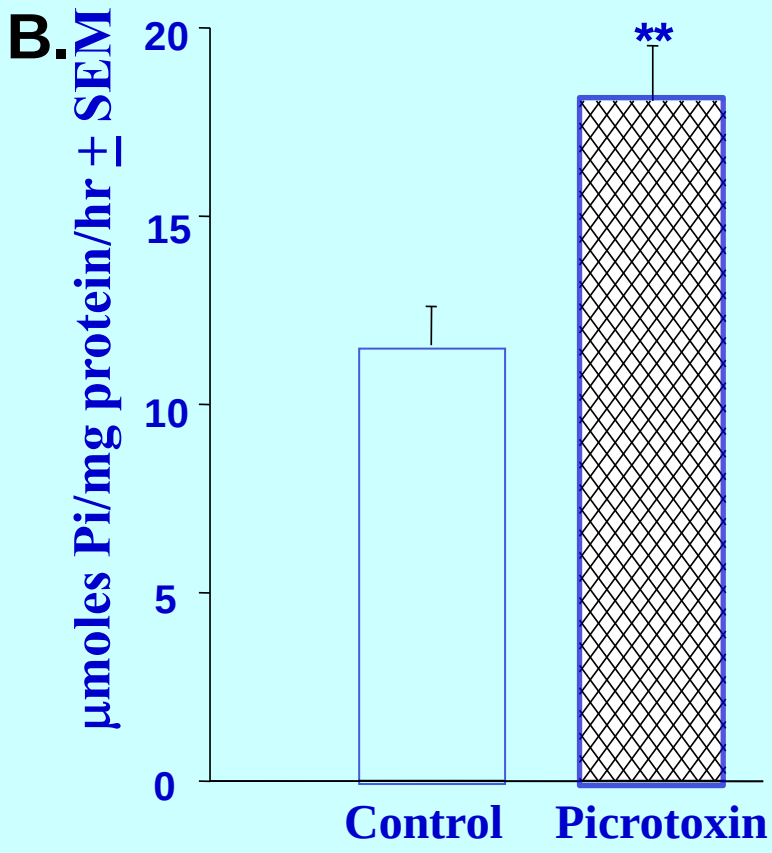
Picrotoxin (every 6h) bilaterally into the LC for 48h reduced REMS (A) and increased Na-K ATPase activity (B) significantly





Kaur et al., Behav Brain Res. 2003

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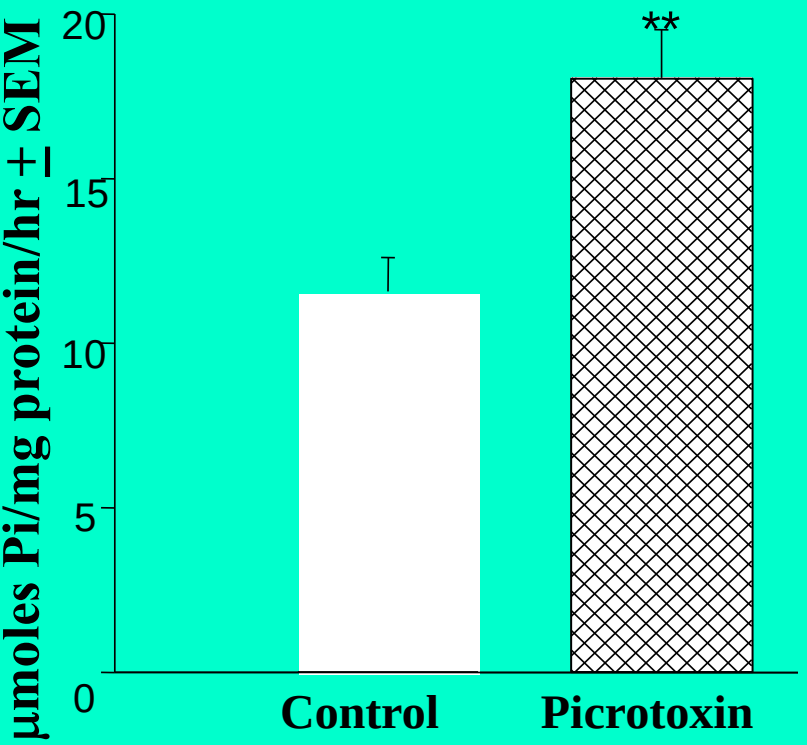
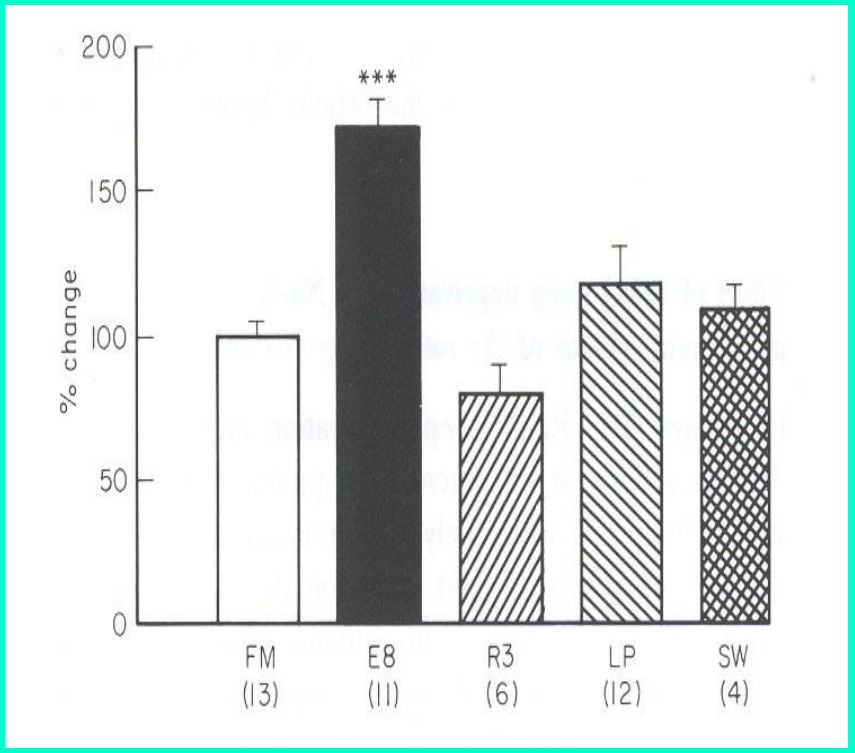
Comparison of Na-K ATPase activity in rat brain

A. **Picrotoxin every 6h into LC**



Kaur et al., Behav Brain Res. 2003

B. **REMSD**



Gulyani and Mallick, J. Sleep. Res., 1993

We had confirmed that the REMS loss associated increase in Na-K ATPase activity is actually mediated by elevated level of NA ***(Gulyani and Mallick, 1995; Mallick et al., J. Neurochem, 2000)***

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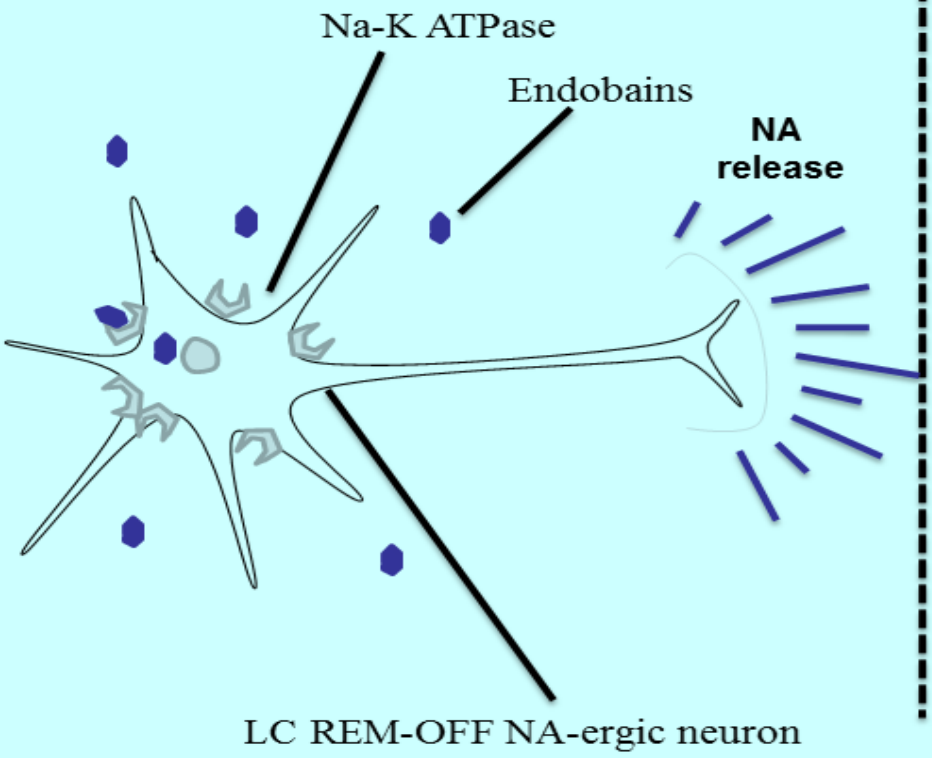
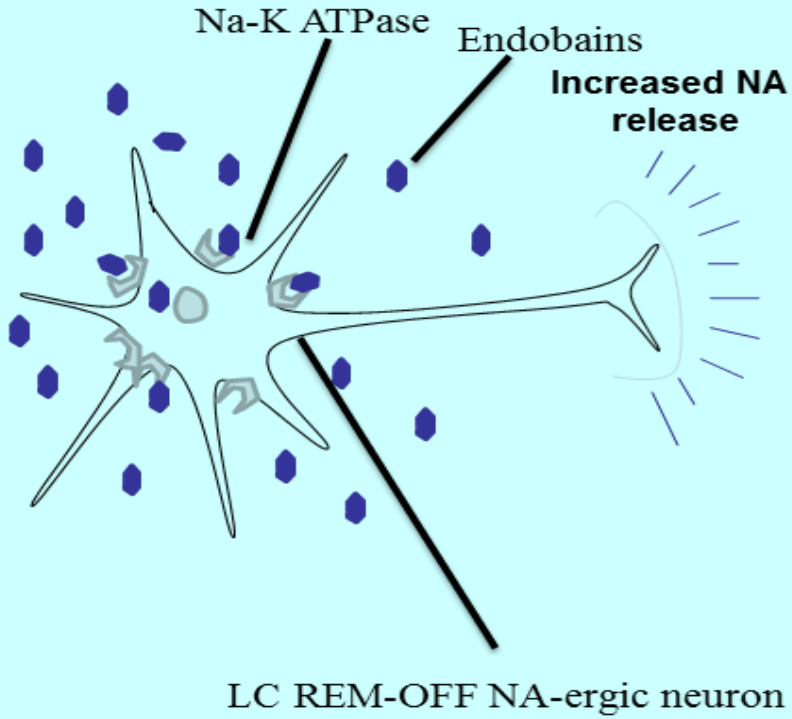
Anti-endobain-antibody into LC and simultaneous recording of waking-sleep-REMS

Normal condition :
Endobains in optimum level



Anti-endobain-antibody will activate LC-REM-OFF neurons



Jaiswal et al., J. Sleep Res., 2009

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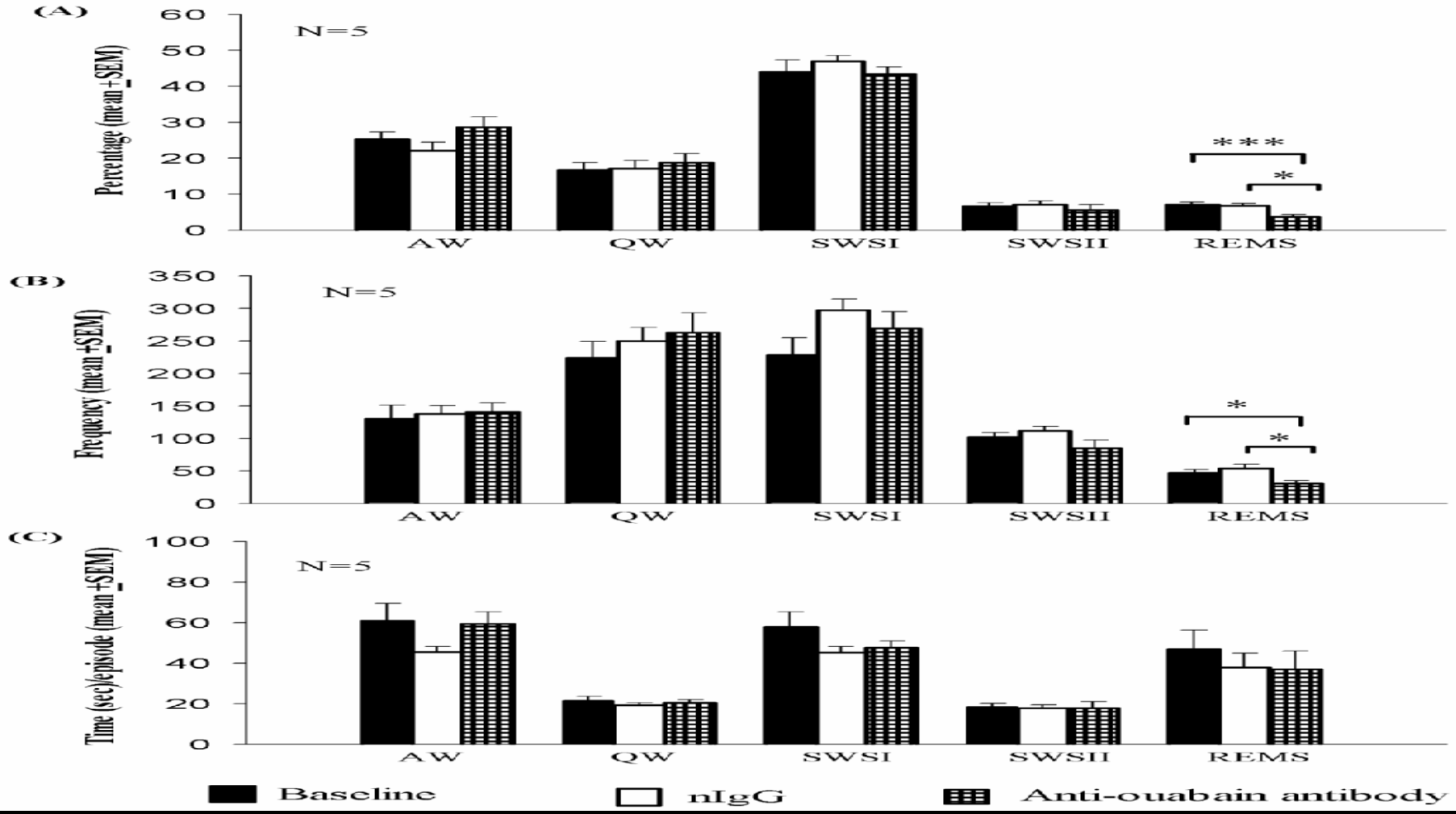
Effect of anti-ouabain antibody into LC on sleep-waking-REMS



Jaiswal et al., J. Sleep Res., 2009

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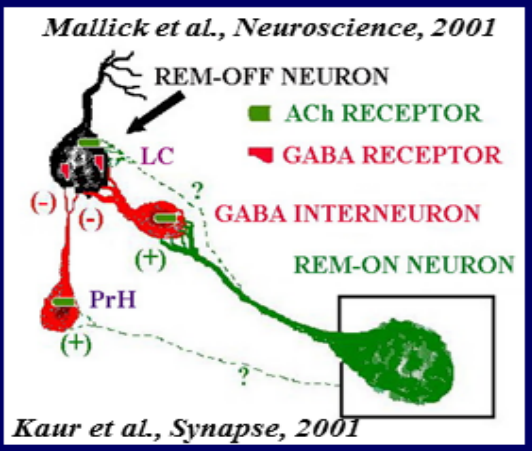
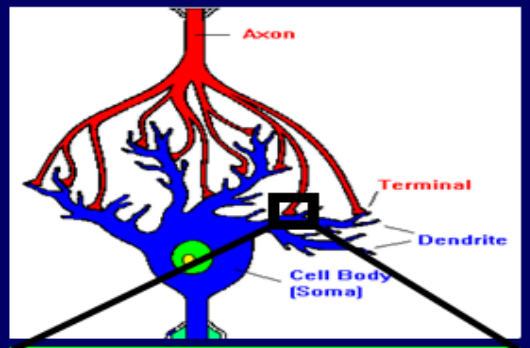
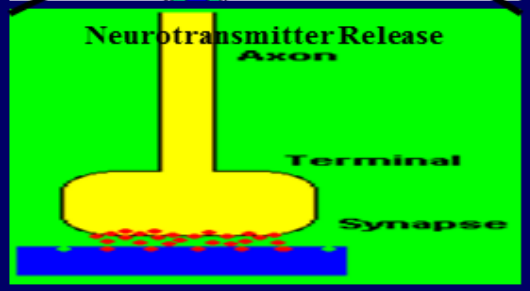
CONCLUSION: TAKE HOME MESSAGE





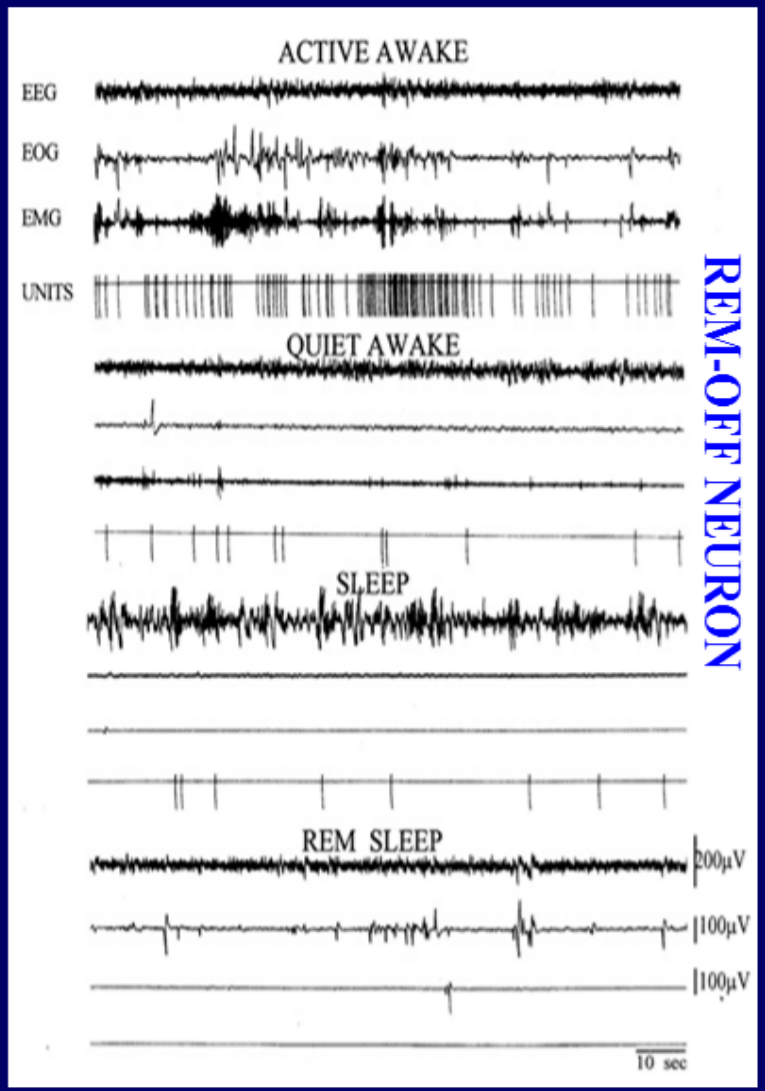


NA-ergic LC REM-OFF NEURONS ARE ACTIVE IN ALL STAGES EXCEPT DURING REMS

THEIR CESSATION BY GABA IS PRE-REQUISITE FOR REMS

NON-CESSATION/ CONTINUOUS ACTIVATION OF REM-OFF NEURONS INDUCES REMS-LOSS AND ELEVATION OF BRAIN NA LEVEL, WHICH IN TURN CAUSES REMS-LOSS ASSOCIATED SYMPTOMS

THUS, UPON REMS LOSS AT LEAST ELEVATED NA IS A PRIMARY CAUSE FOR INDUCING REMSD ASSOCIATED SYMPTOMS



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