

Sleep-related breathing disorders

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This presentation is an educational material for students of the JLF UK in Martin - elective subject Sleep Related Disorders of Breathing and was created based on resources of teachers working at the JLF UK in the past and present, who have participated in teaching the subject.

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Historical perspective

- quite new entity, rapidly developing research field – with technology of recording and analysis
- 1850 – observation of periodic breathing in sleep
- 1870 – UK physicians reported cases of obstructed apneas as “fruitless contractions of the inspiratory and expiratory muscles against glottic obstruction with accompanying cyanosis during sleep”
- 1837 - century several cases of obese persons with extreme daytime sleepiness were described and labeled the “Pickwickian syndrome” (Charles Dickens)
- Early to mid 19th century – periodic breathing was observed in subjects with heart failure by Cheyne and Stokes

Joe Fat Boy

obesity
snoring
daytime sleepiness
fatigue

OSA



Thomas Nast's drawing of the fat boy in "The Pickwick Papers."

Historical perspective

- At the turn of the 20th century periodic breathing was observed in individuals with hypoxia in high altitude
- 1950 - a link between obesity and the control of breathing was fully appreciated as the Pickwickian syndrome was rediscovered - daytime CO₂ retention was observed in obese subjects with daytime sleepiness and without significant lung disease
- 1960 - Bulow reported descriptions of sleep effects on ventilation and ventilatory stability in health
- 1960 - Gastaut defined OSA in obese subjects as intermittent airway obstruction with frequent arousals, providing the first comprehensive links between obesity, sleep-induced airway obstruction, sleep fragmentation, and daytime sleepiness

Rapidly progressing research

- 1980 - reports of
 - 1) sleep effects on brainstem respiratory neurons in unanesthetized, chronically instrumented cat
 - 2) a neuromuscular reflex mechanism maintaining extra-thoracic airway patency in the rabbit
 - 3) sleep effects on reflex control of breathing in the dog and identification of a sensitive CO₂-induced apneic threshold in sleeping humans
 - 4) description of anatomical and neurophysiological determinants of upper airway occlusion in the sleeping human, which provided a unifying “balance of forces” concept of OSA
 - 5) the landmark introduction of CPAP application as the noninvasive treatment for obstructive sleep apnea

Rapidly progressing research

- early in the 1990s, simulation of OSA in rodents using cyclic hypoxia was shown to cause daytime hypertension, initiating research into the long-term cardiovascular consequences
- at this same time, OSA patients were shown to maintain their upper airway patency in wakefulness via a compensatory, augmented EMG activity of their airway dilator muscles
- shortly after the first population study conducted using in-lab studies of sleep and breathing showed a significant prevalence of OSA in a middle-aged, nonclinical population
- it has indicated significant and largely undiagnosed effects of OSA on public health

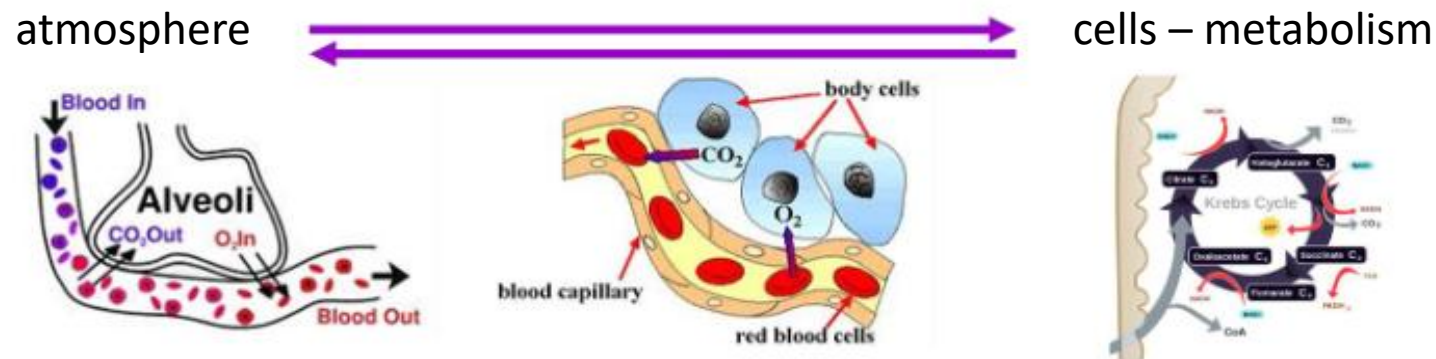
Sleep medicine

- OSA has attracted a myriad of researchers from diverse disciplines and clinical subspecialties
- OSA as a serious, undefined clinical problem has also given birth to many commercial ventures for its diagnosis and treatment, including the building of hundreds of sleep medicine clinics throughout the Western world with the majority of their business concerned with the diagnosis and treatment of OSA
- Finally, given the relatively high prevalence of this sleep-specific problem with potential carryover to daytime pathology, sleep apnea has provided great impetus to the growth of sleep medicine as a clinical and research specialty.

Regulation of breathing

Main function of respiratory system

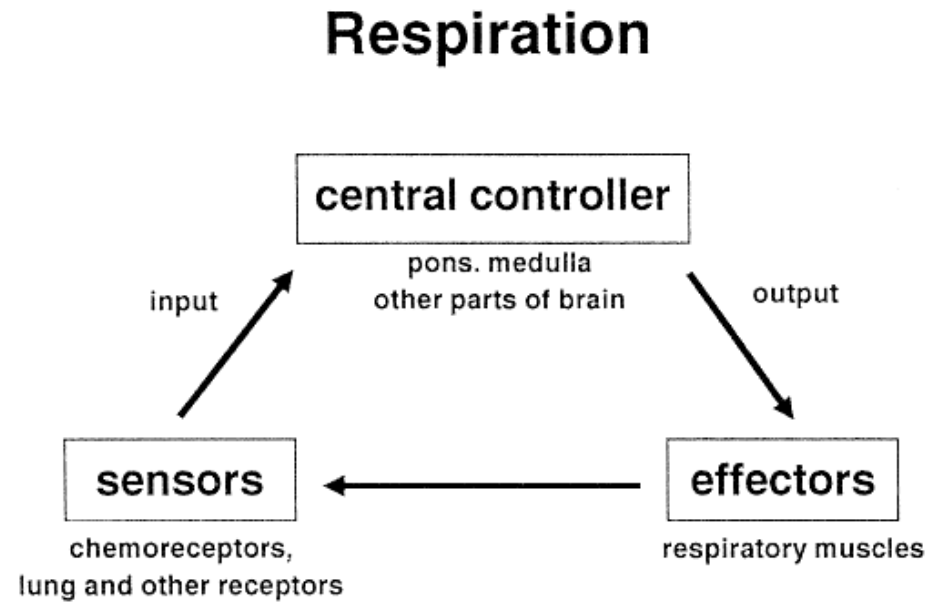
- Provide oxygenation (O₂ transport from the atmosphere to the cells)
- Provide ventilation (CO₂ transport from the cells to the atmosphere)
- By cardio-respiratory coupling



Definition of important processes

- Normoventilation – intensity of respiration that fully matches metabolic demands of the cells, characterized by normokapnia
- Hypoventilation – intensity of breathing is insufficient for metabolic demands of the body, leading to hyperkapnia
- Hyperventilation – intensity of breathing is way higher than metabolic needs of the body, leading to hypokapnia

Regulation of respiration



Neural regulation of respiration

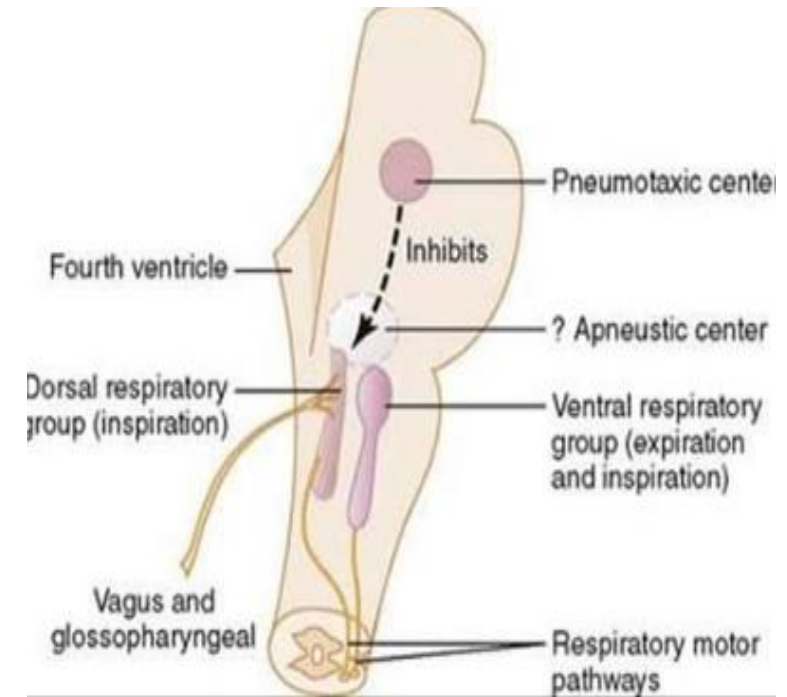
1) Medulla

- Dorsal respiratory group – associated with inspiration
- Ventral respiratory group – associated with expiration.
- Pre-Botzinger Complex - pattern generator, also VRG

2) Pons

Apneustic center – has an excitatory function

Pneumotaxic center - inhibits inspiration



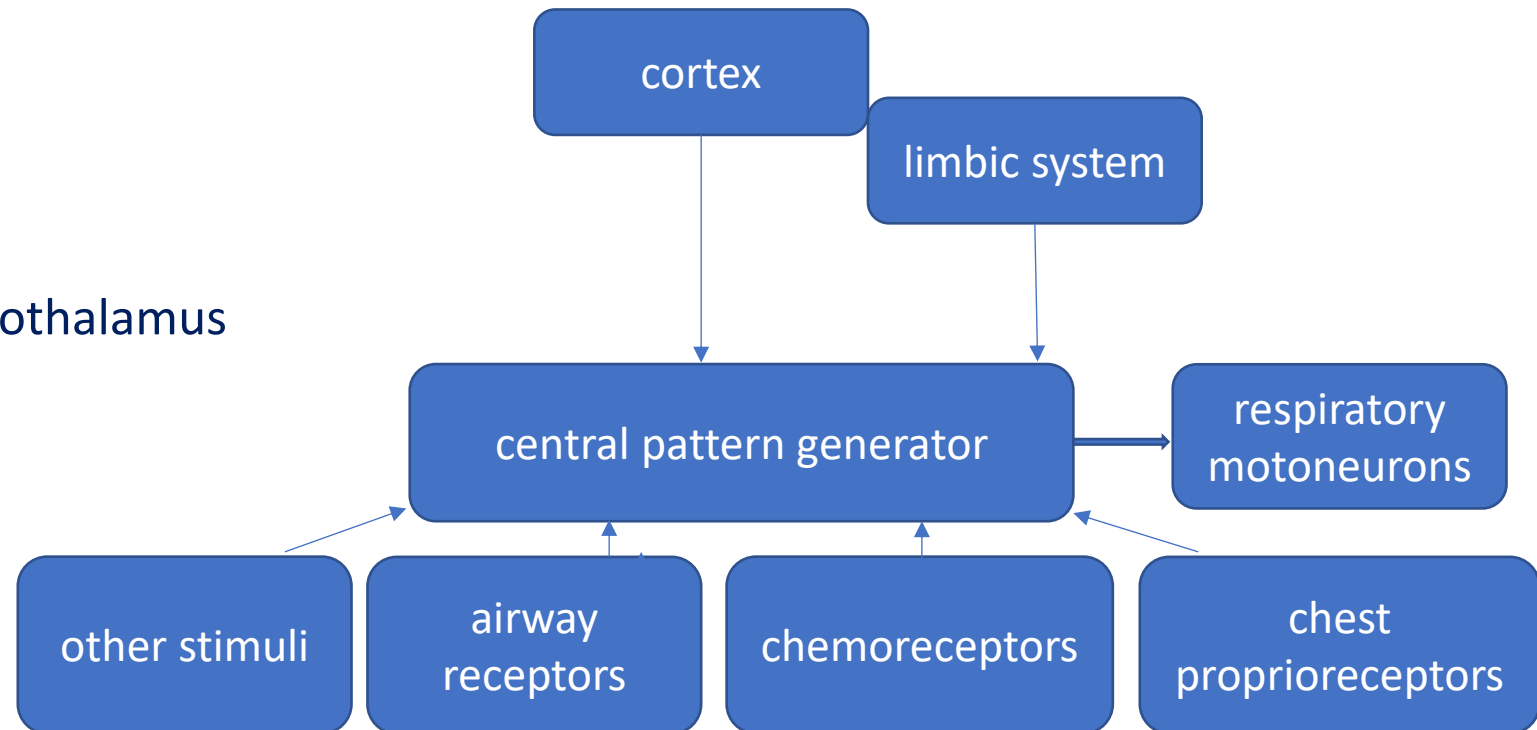
Other parts of the brain modulating respiration

1) Cortex

voluntary control

2) Limbic system and hypothalamus

emotional states

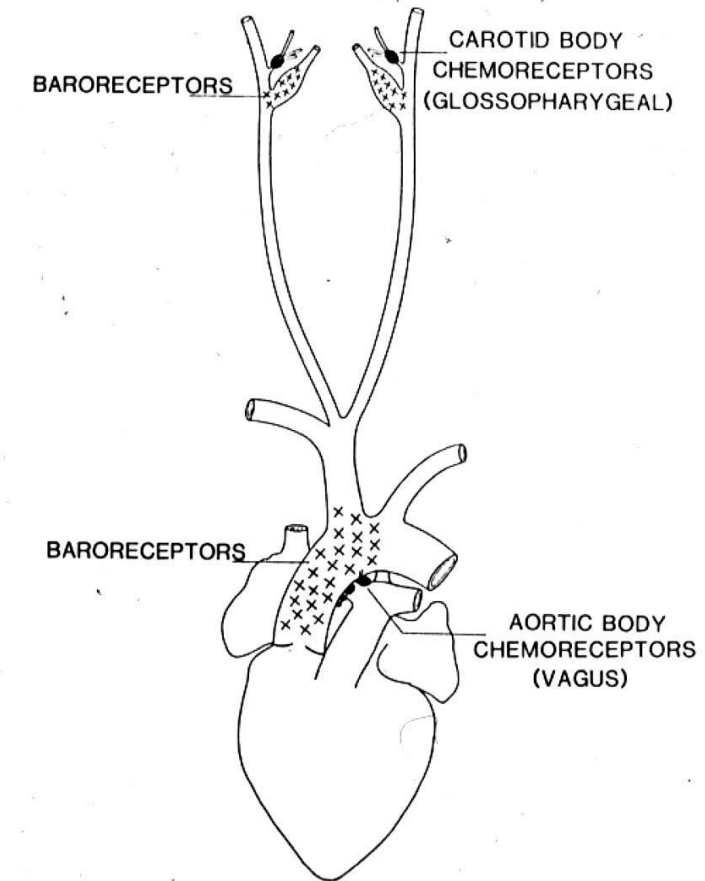


Chemical regulation of respiration

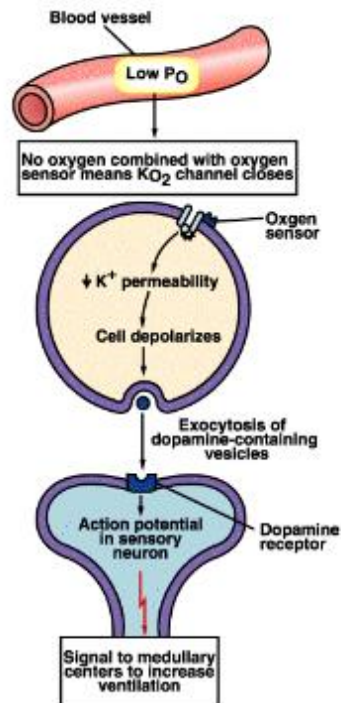
Peripheral Chemoreceptors

Peripheral chemoreceptors are located in both the carotid body and the aortic body. They detect large changes in the **partial pressure of oxygen (pO_2)** as the arterial blood supply leaves the heart. When low levels of oxygen are detected, afferent impulses travel via the **glossopharyngeal** and **vagus** nerves to the **medulla oblongata** and the **pons** in the brainstem. A number of responses are then coordinated which aim to restore pO_2 .

- The **respiratory rate** and **tidal volume** are increased to allow more oxygen to enter the lungs and subsequently diffuse into the blood
- **Blood flow** is directed towards the kidneys and the brain (as these organs are the most sensitive to hypoxia)
- **Cardiac Output** is increased to maintain blood flow, and therefore oxygen supply to the body's tissues

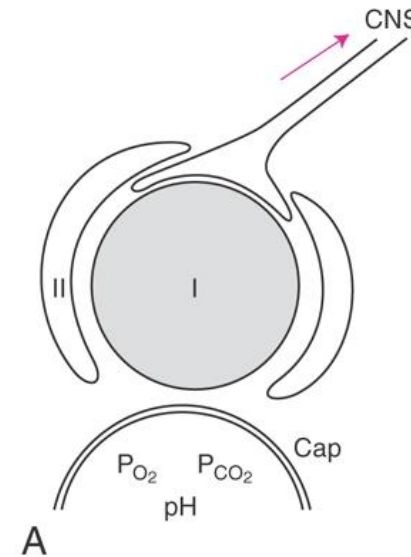


How they detect oxygen level



oxygen sensitive K^+ channels

activated by hypoxemia



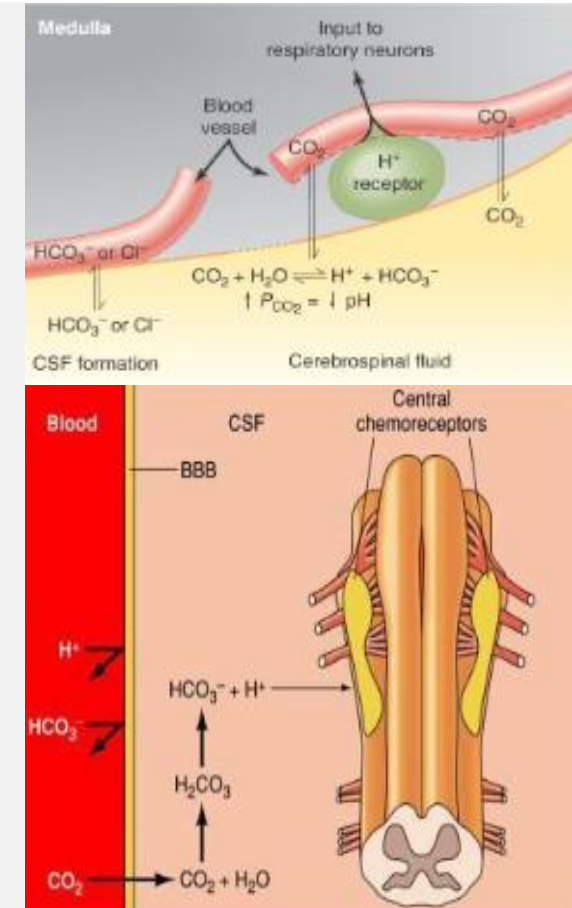
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Central Chemoreceptors

Central chemoreceptors are located in the **medulla oblongata** of the brainstem. They detect changes in the arterial partial pressure of carbon dioxide ($p\text{CO}_2$). When changes are detected, the receptors send impulses to the **respiratory centres** in the brainstem that initiate changes in ventilation to restore normal $p\text{CO}_2$.

- Detection of an increase in $p\text{CO}_2$ leads to an increase in **ventilation**. More CO_2 is exhaled, the $p\text{CO}_2$ decreases and returns to normal.
- Detection of a decrease in $p\text{CO}_2$ leads to a decrease in **ventilation**. Less CO_2 is retained in the lungs, the $p\text{CO}_2$ increases and returns to normal.

The mechanism behind how central chemoreceptors detect changes in arterial $p\text{CO}_2$ is more complex, and is related to changes in the pH of the **Cerebral Spinal Fluid (CSF)**.



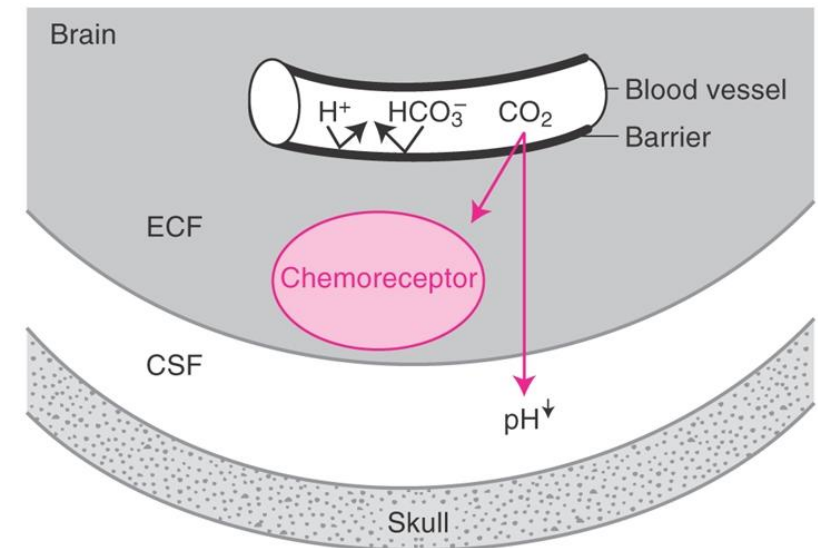
pH Control

The pH of the CSF is established by the ratio of $p\text{CO}_2 : [\text{HCO}_3^-]$.

The HCO_3^- levels remain relatively **constant**. CO_2 freely diffuses across the **blood brain barrier**, from the arterial blood supply into the CSF. CO_2 reacts with H_2O , producing **carbonic acid**, which lowers the pH. This means that the pH of the CSF is **inversely proportional** to the arterial $p\text{CO}_2$.

- A small decrease in $p\text{CO}_2$ leads to an increase in the pH of the CSF, which stimulates the respiratory centres to decrease ventilation.
- A small increase in $p\text{CO}_2$ leads to a decrease in the pH of the CSF, which stimulates the respiratory centres to increase ventilation.

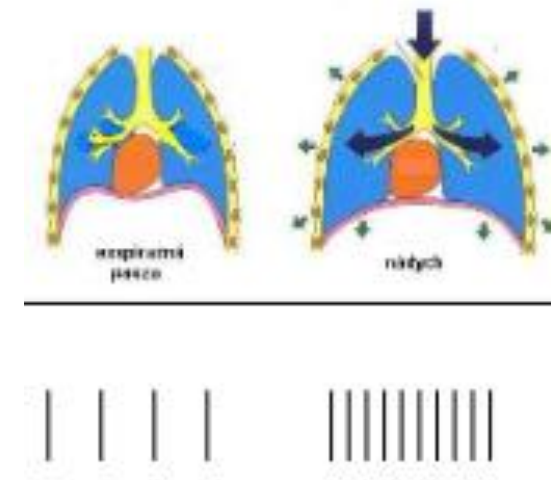
However if $p\text{CO}_2$ levels stay abnormal for a longer period of time, e.g. three days or more, **choroid plexus** cells within the blood brain barrier allow HCO_3^- ions to enter the CSF. Movement of HCO_3^- ions alters the pH which in turn resets the $p\text{CO}_2$ to a different value. This can be relevant in certain diseases, such as Chronic Obstructive Pulmonary Disease (COPD).



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Lung and other receptors

- 1) Pulmonary stretch receptors (also called slowly-adapting pulmonary stretch receptors) Responsible for the Hering-Breuer reflex
- 2) Irritant receptors (also called rapidly-adapting pulmonary stretch receptors)
- 3) J receptors (juxta-capillary receptors)
- 4) Bronchial C fibers

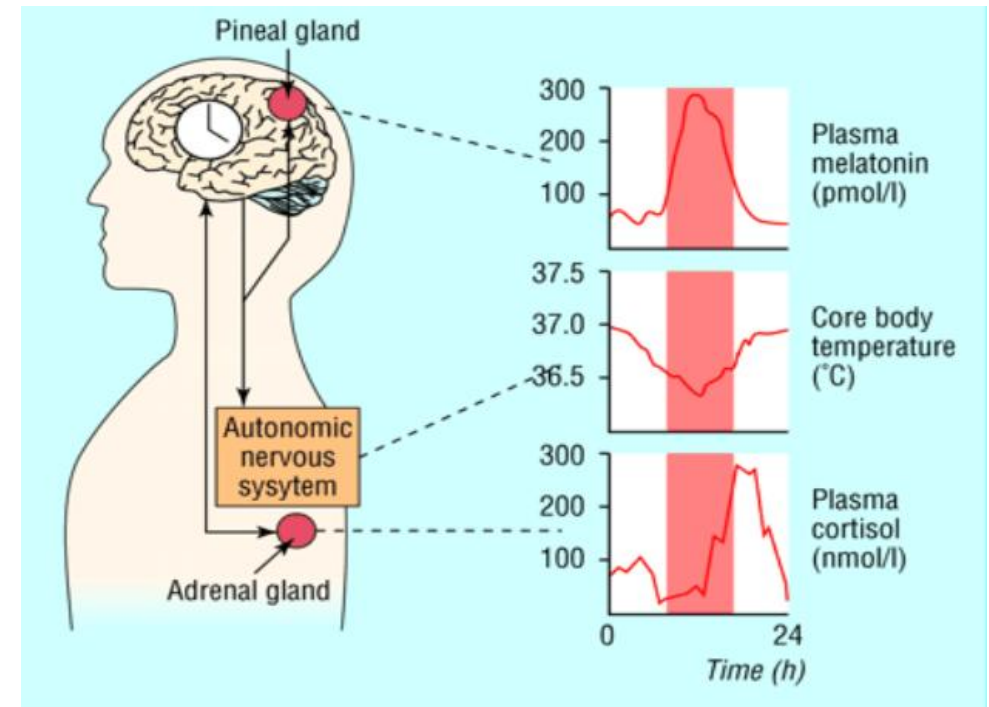


Effects of wakefulness on regulation of breathing

- little or no problems with breathing or airway patency while awake
- majority of people with sleep apnea possess ventilatory control systems capable of precise regulation of alveolar ventilation and ABG with extremely small variations from the norm throughout the waking hours
- these healthy control systems, possess sufficiently sensitive feedback and feedforward controls to ensure precise coordination of
 - chest wall and upper airway “respiratory” muscle recruitment to provide maximum airway diameter
 - low airway resistance
 - optimum lung volumes and respiratory muscle lengths regardless of the ventilatory requirement

Sleep

- most physiological processes in the human body and changes in behavior are subject to biorhythmic fluctuations that are controlled by the hypothalamus
- the biological clock exhibits an effect on neural and endocrine pathways regulating circadian homeostatic rhythms with an approximately 24-hour cycle
- this allows, through homeostasis, the prediction of cyclically recurring changes, an efficient adaptation of the organism to lunar and seasonal changes

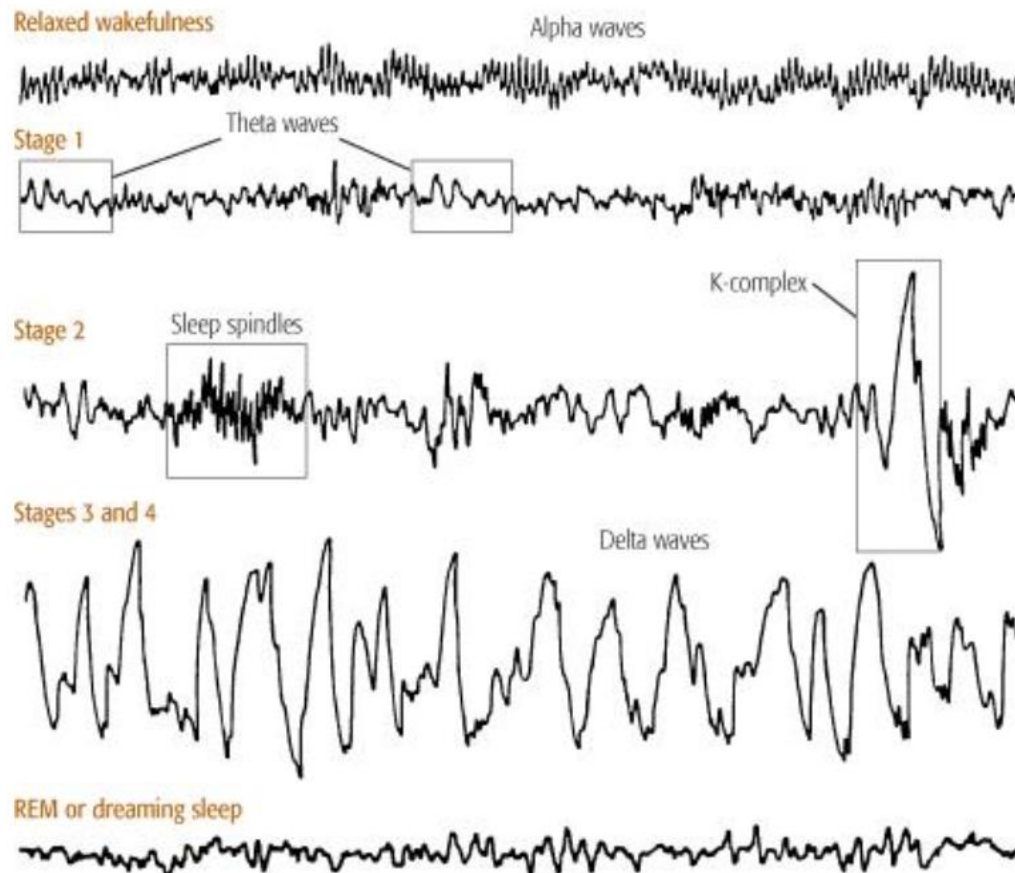


Sleep

Sleep- is a reversible state of reduced response to stimuli and reduced interaction with the environment

- REM - rapid eye movement - paradoxical sleep - (active brain in a paralyzed body), exuberant, illogical dreams, increased metabolism (20%), muscle paralysis, brain commands movement that is not realized, heart and respiratory rates elevated
- after deprivation - anxiety, irritability, tremors, slurred speech, deprivation compensation is complete
- NonREM - SWS - slow wave sleep, orthodox sleep (slumbering brain in a moving body)
- reduced metabolism (10-30%), sleep-walking, sleep-talking, no eye movements, heart and respiratory rate low, EEG high voltages, slow waves, Logically repetitive thoughts, after deprivation - fatigue, compensation for deprivation is partial

Sleep



EEG recordings identify several stages of sleep

Wakefulness with closed eyes - alpha waves (relaxed wakefulness)

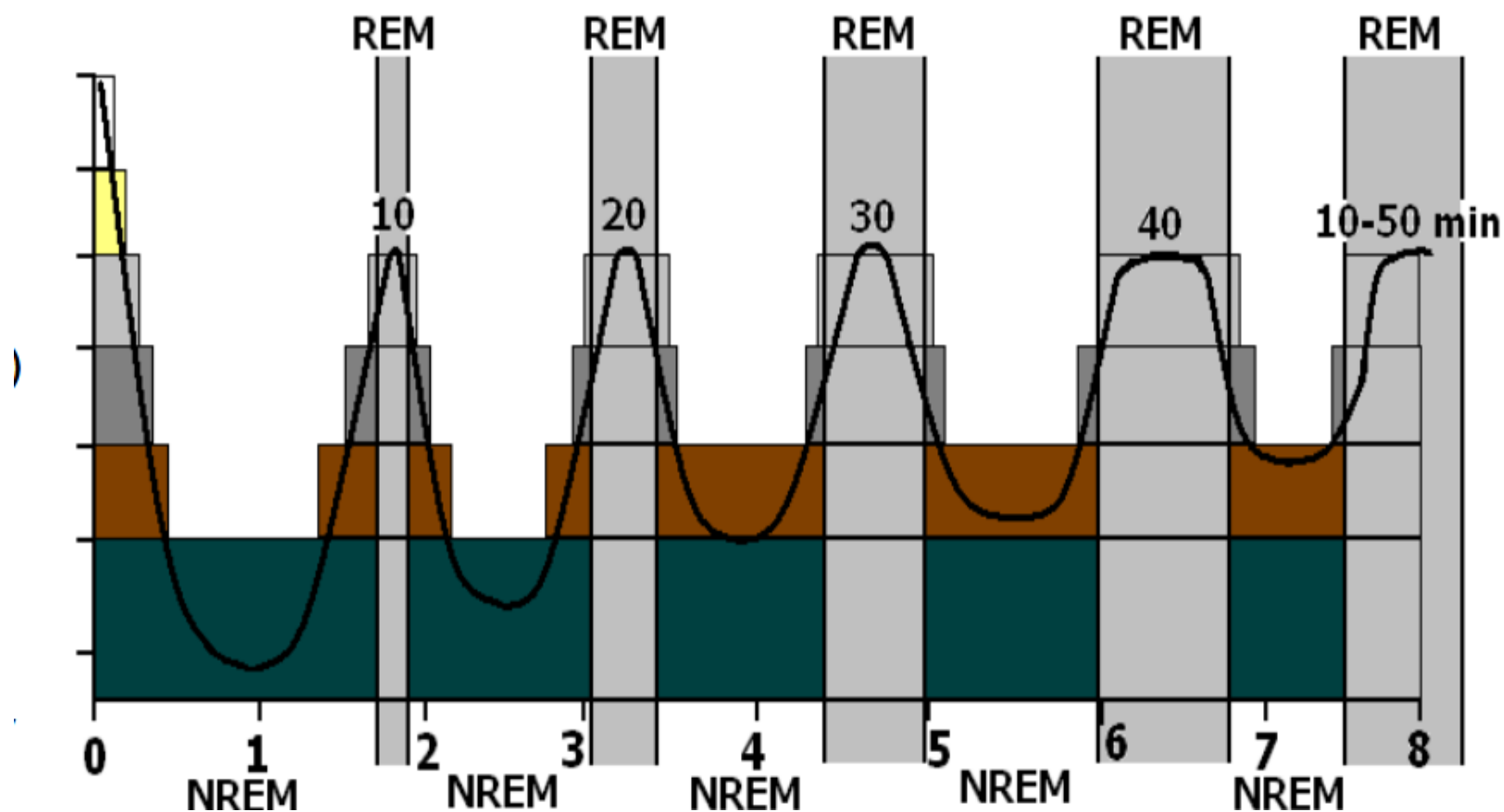
Theta waves are typical for stage 1 of NREM

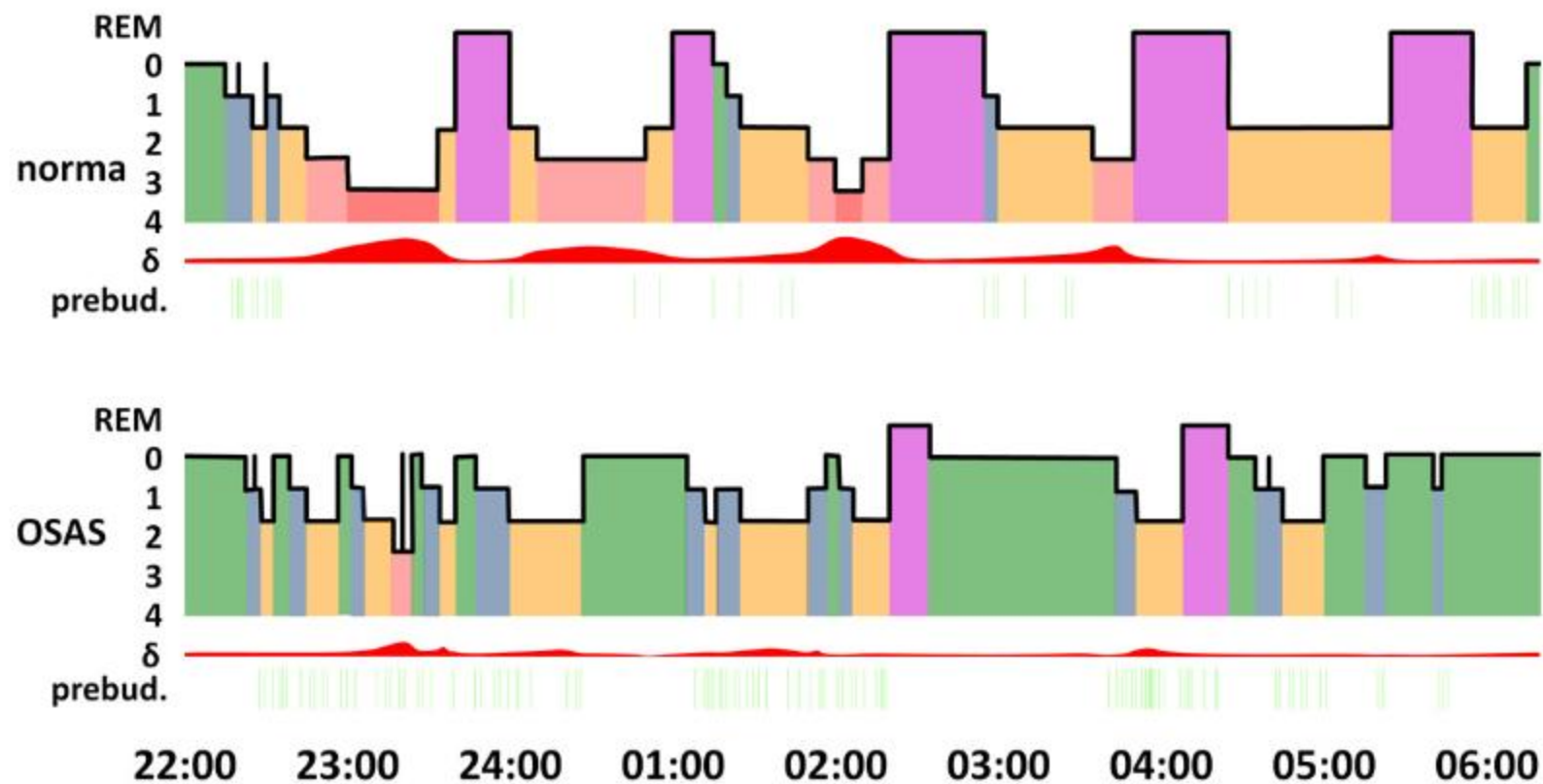
Stage 2 of NREM is interrupted by sleep spindles and K complexes

Stages 3 and 4 of NREM is deep sleep characterized by slow waves with high amplitude

REM sleep resembles wakefulness

Sleep architecture





Effect of sleep on respiration



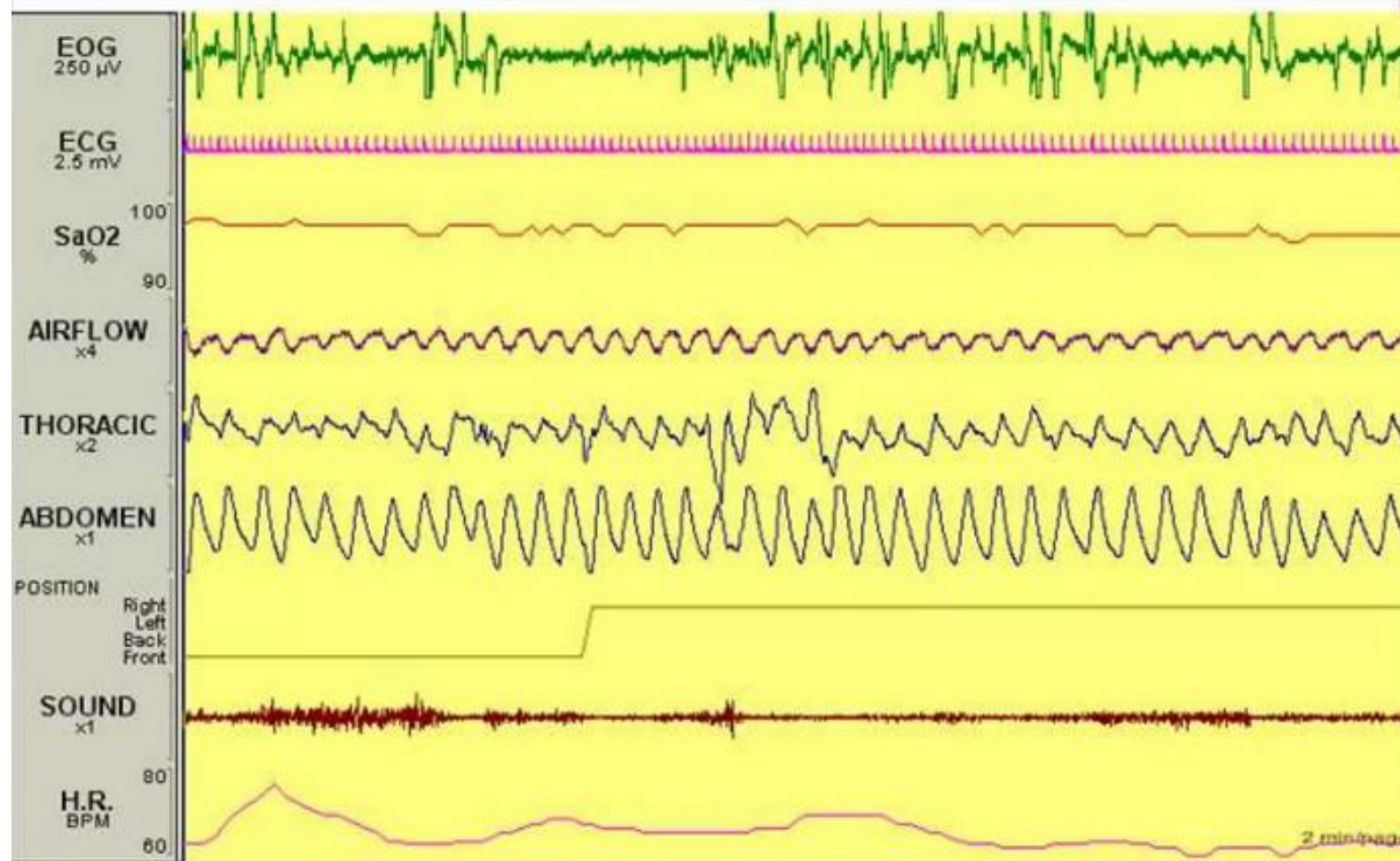
Consider influences of sleep on the control of breathing.

- el. activity from INS neurons, EMG activity of diaphragm and abductor muscles of the upper airway show reductions in amplitude upon the transition from awake to NREM sleep, followed by mild to moderate hypoventilation and increases in UA resistance
- sleep induces greater reductions in the EMG activity in the UA versus chest wall pump muscles
- a fast and highly variable RR is a hallmark of REM sleep in mammals, even though postural muscles, including accessory respiratory muscles of the chest wall, are essentially atonic therefore
- a drive to breathe is common in REM coincident with increased diaphragmatic EMG activity and increased activity in resp. neurons above those levels observed in NREM or wakefulness

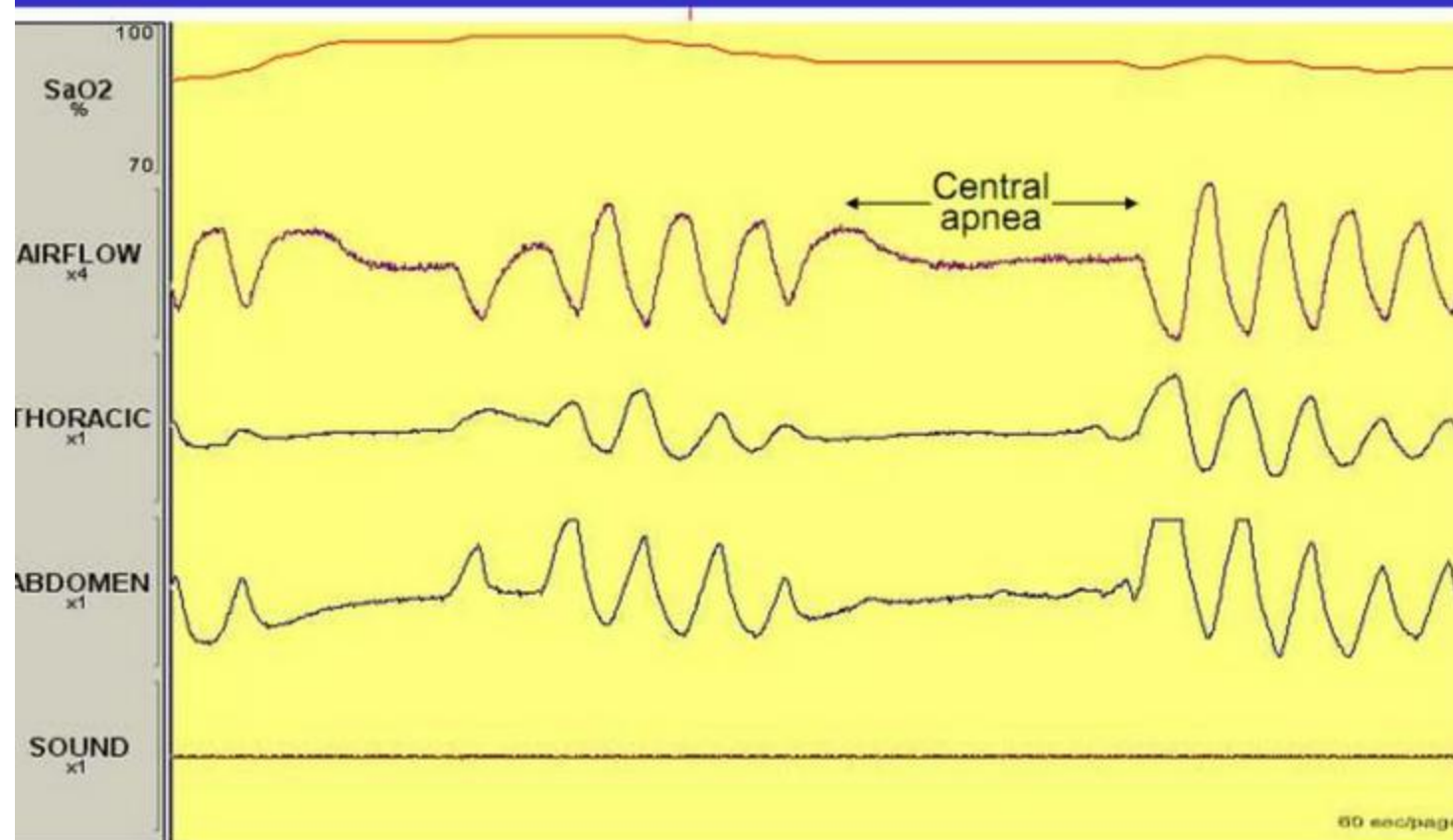
Consider influences of sleep on the control of breathing

- Pa_{CO_2} can be lowered substantially (using mechanical ventilation) during wakefulness with little or no disruption of breathing pattern; but in NREM, minimal reductions in Pa_{CO_2} result in apnea
- partial ablation of the rat's pre-Bötzinger complex, does not affect breathing pattern or chemoresponsiveness in wakefulness but is followed by apnea and ataxic breathing in sleep
- focal acidification of the retrotrapezoid nucleus (chemosensors), produces a significant ventilatory response in wakefulness, with no response in sleep
- mechanical or chemical stimulation of the larynx or intrapulmonary airways causes cough in wakefulness but not in sleep, implying that acts requiring complex coordination of glottal, intercostal, diaphragm, abdominal, and tracheobronchial muscles require the participation of higher structures that are active while awake but not in sleep

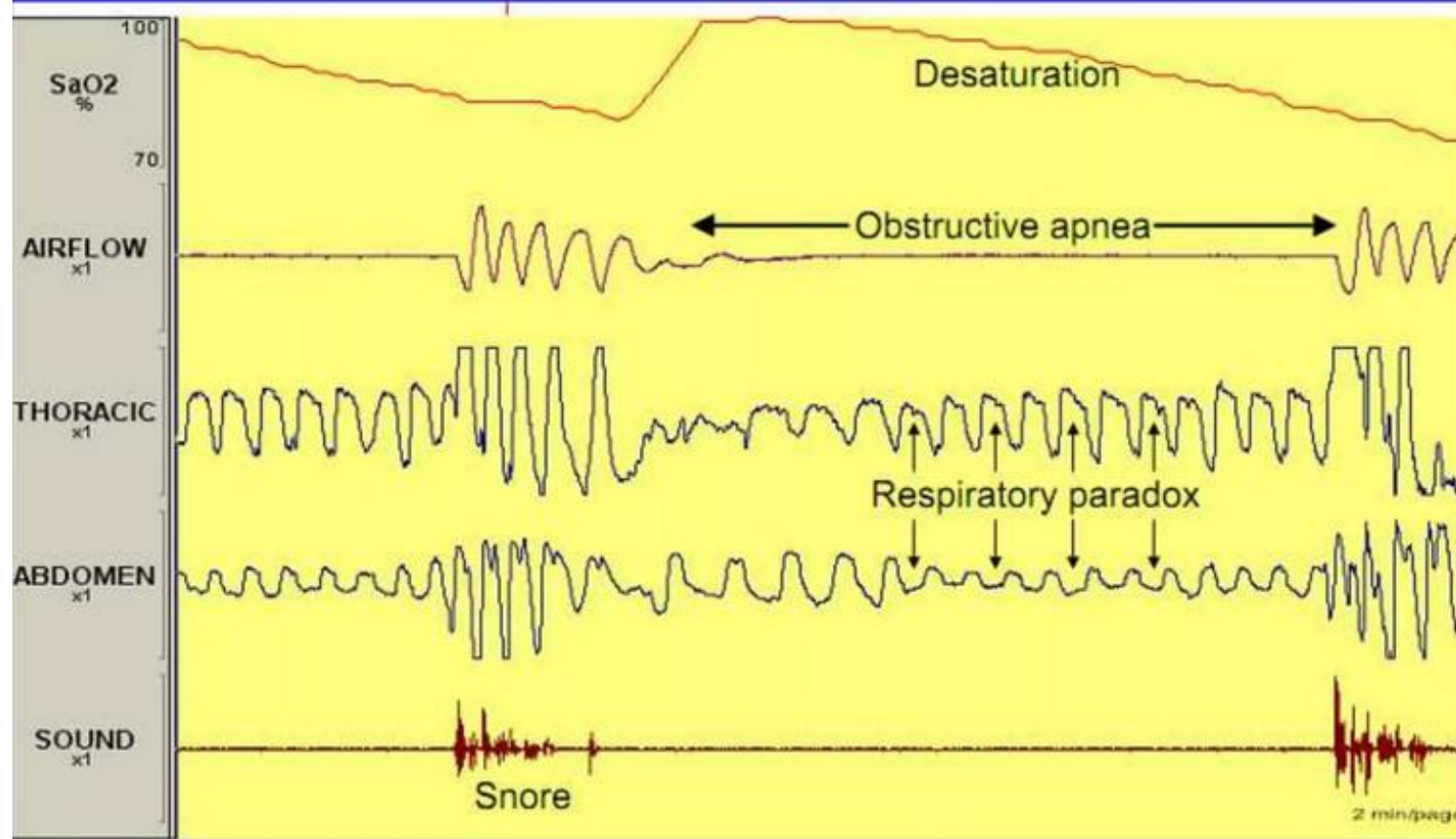
Normal Sleep Study



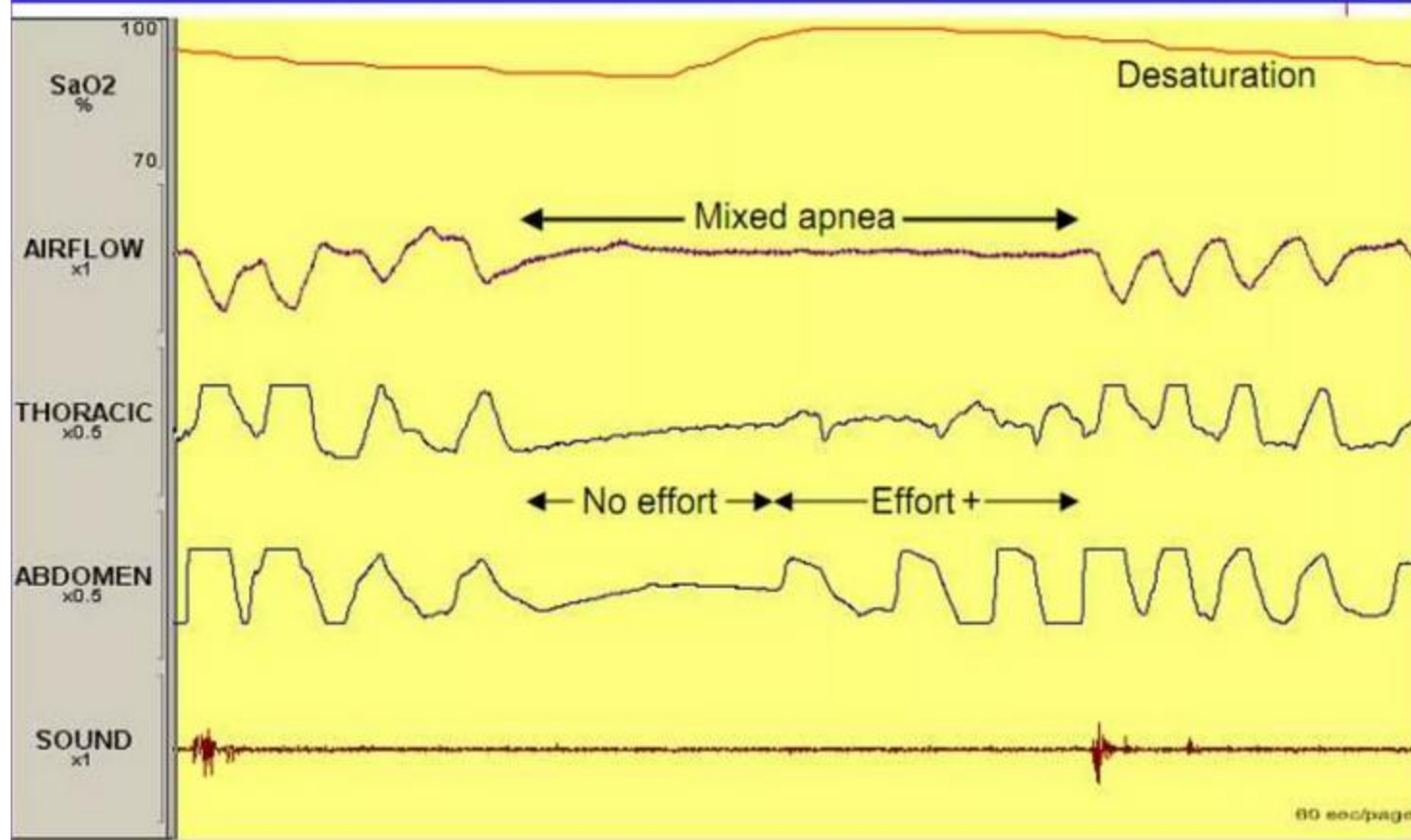
Central apnea: Complete cessation of respiratory effort and airflow



Obstructive apnea: Complete cessation of airflow despite efforts to breathe



Mixed apnea: Complete cessation of airflow with gradual increase in respiratory effort after an initial absence



Hypopnea: Reduction in airflow compared to baseline, associated with desaturation

