공황장애의 새로운 생리학적 이해

- 호흡, 산염기 균형을 중심으로 -

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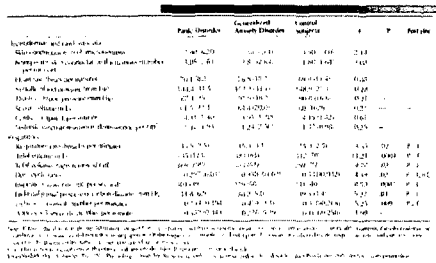
- Physiological Mechanism of Breathing
- Physiological Mechanism of Acid-base Balance
- Panic Disorder and Respiratory System Dysfunction
- Panic Disorder and Panicogen Sodium lactate

Background

- Classification of Panic Disorder (Biber and Alkin 1999)
  - non-respiratory subtype
  - respiratory subtype
    : symptom profile of panic attacks
    : sensitivity to the CO2
- Biological challenge test ; sodium lactate and bicarbonate, norepinephrine, yohimbine, caffeine, isoproterenol, inhalation or re-breathing CO2 and O2 mixture

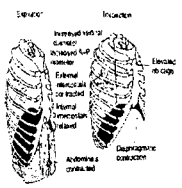
Background-Evidence of Subtype

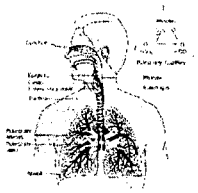


- Greater tidal volume variability including sighs
- Slowness to recover from voluntary hyeperventilation
  - slow pCO2 recovery from hyperventilation is a highly sensitive and specific to PD
- Life time prevalence of respiratory disease is higher in PD than other AD
- Higher prevalence of PD in COPD
- Asthma is associated with a high risk of panic attacks and panic symptom

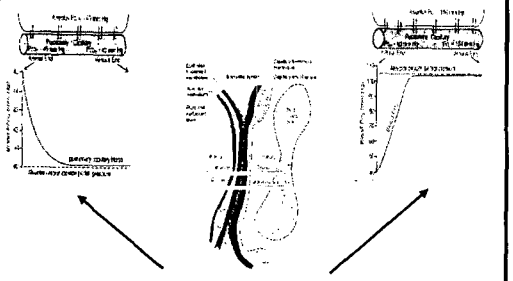
Breathing

- **Ventilation : process of moving air in and out of the lungs, basically passive**

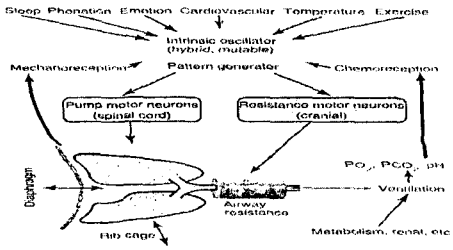




Gas Exchange



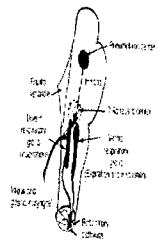
CNS controls of Breathing



Respiratory Control Center

Breathing – automatic process
; normal frequency 14/minute
; average tidal volume 500 ml
; minute ventilation 7 l/min

Center for basic respiratory rhythm – neurons of medulla and pons
; *synaptic input from cortical and potine neuron*



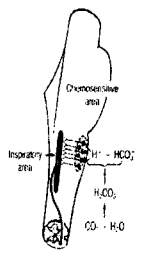
- Dorsal respiratory group of neurons
  - inspiratory and rhythmical function
  - nucleus of the tractus solitarius
- Pneumotaxic center
  - limiting the duration of inspiration and increasing respiratory rate
- Ventral respiratory group of neurons
  - both inspiration and expiration
- Apneustic center – operate in association with the pneumotaxic center to control the depth of inspiration

Chemical Control of Respiration

- Chemosensitive area of respiratory center
  - located bilaterally lying less than 1 millimeter beneath the ventral surface of the medulla
- Oxygen(O_2) – unimportance of oxygen for direct control of the respiratory center
- Hydrogen ion (H^+) – primary stimulus
  : do not easily cross either the BBB or Blood-CSF barrier
  : less effect in stimulating the chemosensitive neurons
- Carbon dioxide(CO_2) – stimulating the chemosensitive area

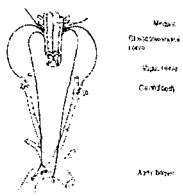
Importance of Pco_2

- Very little direct effect, but very potent indirect effect
- CO_2 passes through BBB and Blood-CSF barrier
- Blood Pco_2 reacts with the water to form hydrogen ions → released into the respiratory chemosensitive sensory area
- Importance of CSF Pco_2 in stimulating the chemoreceptiove area
  - excitation more rapidly
  - very little protein acid-base buffers than brain tissues



Peripheral Chemoreceptor System

- Carotid bodies (largest number), aortic bodies (sizable number)
  - exposed at all times to arterial blood, not venous blood
  - oxygen concentration in the arterial blood falls below normal → chemoreceptor stimulated
  - CO_2 and H^+
    ; respiration center(7*) > chemoreceptor
    ; five times rapidly than central stimulation



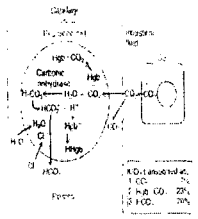
Acid-Base Balance

- 산과 염기의 정의 : 어떤 물질이 용액에서 용액으로 H^+ 을 유리하는 것을 산이라 하고, 반대로 H^+ 와 결합하여 용액내의 H^+ 의 농도를 감소시키는 것을 염기라 한다
- Volatile acid input : CO_2와 같이 수용액에서 일부 H_2CO_3로 존재하나 Pco_2가 낮은 곳에서는 다시 CO_2로 변하여 수용액으로부터 소실된다. 즉 폐를 통해 배설
  - RBC contain carbonic anhydrase

    $CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$

    : H^+ are buffered by hemoglobin, bicarbonate leaves RBC in exchange for chloride

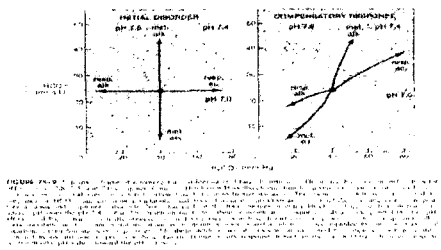
- Volatile acid output
  - CO_2 formed by cellular respiration
  - during blood transit through the lungs, *bicarbonate reenters RBC and* combines with protons to form carbonic acid → dissociate to CO_2 and water
  - CO_2 diffuse freely through RBC and alveolar epithelium



Relationships between HCO_3^- and Pco_2 in Simple Acid-Base Disorders

Condition	Primary disturbance	Predicted Response
Metabolic acidosis	↓HCO_3^-	Pco_2 ↓
Metabolic alkalosis	↑HCO_3^-	Pco_2 ↑
Respiratory acidosis	↑ Pco_2	HCO_3^- ↑
Respiratory alkalosis	↓ Pco_2	HCO_3^- ↓

Frame of Reference for Considering Acid-Base Disturbance



Lactate Infusion and Panic Attack

- Original observation : IV lactate produce panic anxiety in susceptible patients but not in normal subject
  (Pitts and McClure, 1967)
- Reliability of panic provocation by sodium lactate
  (Papp et al, 1993)
- Specific panic disorder compared with other anxiety disorders and psychiatric condition
- lactate + NAD $\overset{LDH}{\rightleftharpoons}$ pyruvate + NADH → $CO_2 + H_2O$

  NAD : nicotine adenine dinucleotide,
  LDH : lactic acid dehydrogenase

- System alkalosis -> vasoconstriction of cerebral vessels -> cerebral ischemia
- Rapid passive elevation in the lactate : pyruvate ratio in localized brain regions outside BBB

→ lower the intracellular pH in medullary chemoreceptor
(dysregulation in medullary chemoreceptor = greater sensitivity to alteration in pH)

- Metabolic alkalosis → metabolized bicarbonate → metabolized to CO_2 → penetrate CNS → increase p CO_2

→ ventral medullary chemoreceptor stimulation → increase ventilation rate

→ profound stimulus for locus coeruleus activation → central noradrenergic activation → panic attack **(lactate -CO_2 theory)**

CO_2 Challenge and the Elicitation of Panic

- Drury(1919) - " irritable heart syndrome "
  ; more sensitive to inhalation CO_2 than healthy control
- Cohen and White(1950) – " neurocirculatory asthenia "
  ; 4% CO_2 mixture for 12 min → anxiety attack, not in control
- Exposure to High concentration of CO2 → intense bodily sensation and panic attack more often in patients with PD, *not in individual with other anxiety disorder or in* healthy control

Challenge Method

- ***Steady-state method***
  - continuous exposure to a steady-state level of CO_2 (typically 5-7%) in a respiratory canopy with room air
  - clear plastic hood is fitted over the patient's head
  - breath the gas mixture for a period of 10-20 min until a panic attack occurs

  * continuous positive air delivery, mixtures of CO_2 (typically 5.5%) balanced with air through a mask, 15min

- **Read re-breathing technique** (Read, 1967)
  - re-breath (breath in and out of a closed system) gas through a mouthpiece, while patient's nose is occuled by a noseclip
  - CO_2(typically 5-7%) is usually balanced with O_2 (93-95%)
    " hyperoxic hypercapnic procedure "
  - CO_2 concentration in the system gradually increases
  - CO_2 level rise rapidly, usually reaching approximately 7-9% within the 3-5 min

- **Single- or double-breath inhalation**
  - one or two vital capacity inhalations (maximum volume of air one can inhale after a maximum exhalation) of 35% CO_2 balanced with 65% O_2
  - gas mixture is delivered through through a mask covering the nose and mouth
  - highest level of systematic CO_2 exposure among the three methods CO_2 delivery, albeit for the shortest time

CO_2 Hypersensitivity

- Biological cause of panic initiation
  " False suffocation alarm " theory of panic (Klein 1993)
  - hypersensitive to CO_2, with blood CO_2 levels lower than those healthy controls
  - the brain's suffocation monitor erroneously signals a lack of useful air, thereby maladaptively triggering an evolved suffocation alarm system

  → "evolutionarily derived set-point has become dysfunctional "
  → hypersensitivity instigate spontaneous panic attacks in a variety of common situation in life where one's level would slightly rise

- Neuroanatomical site for deranged suffocation alarm system → parabrachial nucleus of the solitary tract
- Elevated p CO_2 → activation of vagus nerve → nuclues tractus solitarius → stimulate locus coeruleus and provoke hyperventilation (Papp et al, 1993)
- Psychosocial theory of CO_2 challenge
  CO_2 induce physical sensation → catastrophically misinterpreted and catastrophised as panic
  → amplify anxiety response → fear conditioning of aversive stimuli

Limitation of CO_2 Hypersensitivity

- Have not tested the sensitivity of the peripheral chemoreflex → both CO_2 and O_2 sensor are important sensor of suffocation
- Practical difficulty gathering data from naturally occurring panic attacks (unpredictable, not occur on a test day even when 24-h monitoring is done)
- Substantial variability among studies in the rated of CO_2-induced panic attack
- Lack of standardization on important methodological parameters

결 론

- 공황 발작 및 장애는 호흡기 기능의 이상과 연관이 있다.
- 공황발작 및 장애는 pCO_2 hypersensitivity, misinterpretation and catastrophication of physical sensation, false suffocation alarm system 등이 고려되고 있다
- 공황발작 및 장애는 lactate and bicarbonate infusion에 의한 metabolic alkalosis 및 pCO_2의 증가와 연관이 있다
- 공황장애의 CO_2 challenge test로는 steaday-state method, Read re-breathing technique, single- or double-breath inhalation이 있다
- 우리나라의 공황장애 환자의 호흡기 이상에 관한 향후 추후 연구가 필요하다

감사합니다 !!