Renal TRanspoRT pRocesses foR oRganic subsTances

Glucose: It is reabsorbed from the PCT via an active transport system. It is transported against a concentration gradient (at normal plasma levels of approximately 100mg/dl plasma, all of the filtered glucose is reabsorbed) by a process requiring metabolic energy with glucose not being chemically altered during reabsorption. The hexose can be reabsorbed up to a maximal rate and when glucose load exceeds this reabsorptive limit, it is excreted into urine.

Amino Acids: Amino acids are reabsorbed by several discrete active transport systems. Basic amino acids like lysine, arginine, histidine share a common tubular transport system and competition among them exists. Other amino acids transport systems include that of leucine and isoleucine; and that of proline, hydroxyl proline and glycine. Amino Acid reabsorption requires the presence of pyridoxal phosphate. A complex is formed by the amino acids, pyridoxal phosphate and a metallic iron (Mg^{2+}) which probably facilitates the transport of amino acids from the tubular fluid into the intracellular pool of amino acids and subsequently into the peritubular blood flow.

Uric acid: It is formed from the degradation of purines, adenines and guanine. Apart from humans and higher apes, mammals convert uric acid to allantoin by the action of the enzyme uricase. Allantoin is water soluble and is rapidly excreted into urine primarily by glomerularfiltration. Uric acid or Na urate is excreted into the urine through a combination of glomerular filtration, tubular reabsorption and tubular secretion. Urate has limited solubility in water and its reabsorption is governed by its relationship between pH of tubular fluid, pKa of urate and concentration of urate in plasma and tubular fluid.

Diagram of Na-K-ATPase pump

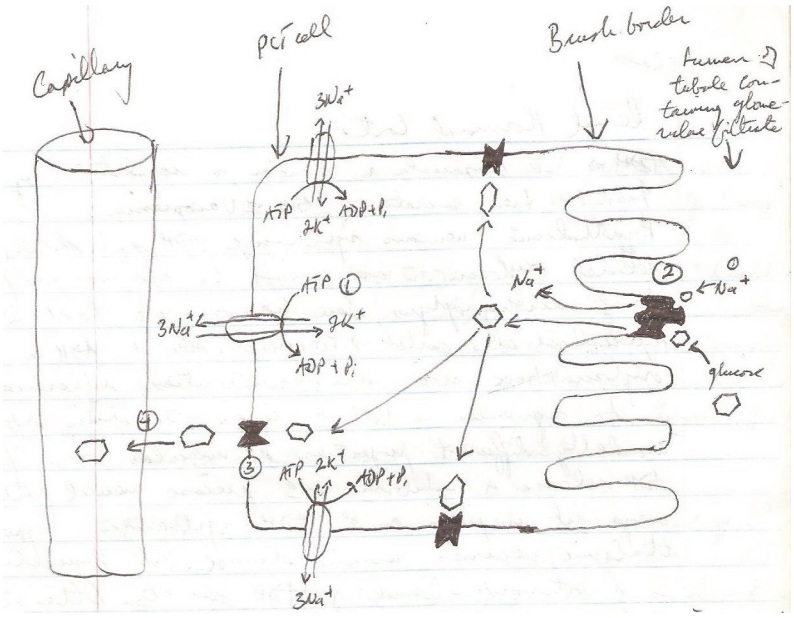

Diagram of active transport of Glucose

1. Na^+ - K^+ pump, pumps out Na^+ and reduce concentration of Na^+ inside cell.
2. A special transport protein reabsorbs both Na^+ and Glucose. Such proteins are called symporters (the movement of the 2 molecules is linked). Na^+ and glucose are effectively moving down diffusion gradient, but this is only made possible by the active transport of Na^+-K^+ pumps. The process is therefore sometimes referred to as secondary active transport.
3. Glucose leaves the cell by facilitated diffusion through the carrier protein.
4. Glucose diffuses into the blood capillaries. Amino acids and some other nutrients follow the same type of route.

Renal HoRmonal ContRol

Antidiuretic Hormone: Water conservation or secretion is regulated by increased or decreased secretion of ADH (aka- Vasopressin). Hypothalamic neurons and the closely related oxytocin, which are carried by axoplasmic flow to the neuro-hypophysis, where hormones are stored in specialized cells called pituicytes. Although ADH and oxytocin have close structural similarities, differences in amino acid sequences in both the ring and side chains confer markedly different properties. The molecular basis for ADH release or inhibition and the precise neural pathways that impinge on the ADH-synthesizing hypothalamic neurons remains elusive.

Water deprivation is the strongest stimuli for ADH secretion. Other stimulus include, fear, increase in extracellular fluid volume and pain. Drugs may also alter the rate of ADH secretion

e.g. ethanol which is the most abused but legally available C.N.S. depressant. This ethanol is a potent inhibitor of ADH secretion.

ADH acts on the distal portions of the nephron, most prominently on the collecting duct to alter their permeability to water and urea. When ADH secretion is enhanced, the CD is increasingly permeable to H_20 and urea and they more easily diffuse from the tubular fluid of the CD into the hyper-osmotic medullary interstitium and vice versa.

If the hypothalamo – neurohypophyseal system is destroyed, a syndrome known as diabetes insipidus is produced, which is characterized by excretion of large quantities of water. Inappropriately high concentration of ADH, whether induced iatrogenically or by secretion of ADH by some cancers results in dilution of serum electrolytes, particularly sodium leading to dilutional hyponatremia. This problem may be augmented by the ability of high levels of ADH to promote renal Na excretion.

Aldosterone: it's the recognized primary mediator of the renal regulation of Na and K^+ equilibrium. This function is due to a direct tubular effect of the hormone that permits normal rate of Na reabsorption and K excretion. The areas of the nephron that are sites of aldosterone secretion have not been determined conclusively, although the distal segments have been implicated i.e. DCT and CD.

Excessive secretion of aldosterone or the long time administration of a mineralocorticoid steroid to dogs or humans results in Na retention for a period of 5-7days, as high levels of mineralocorticoid activity are maintained, 'escape' from Na retention occurs in the form of a saline diuresis. The functional processes that are involved in the escape phenomenon are not yet known. The site of production of aldosterone is the adrenal cortex.

Parathyroid hormone: Ca and phosphate excretion into urine is regulated by this hormone. PTH is synthesized by the parathyroid gland and thyrocalcitonin is synthesized by the thyroid gland. PTH causes a decrease in the phosphate reabsorption and an increase in phosphate excretion in the urine. These changes are due to direct tubular effect. The administrationof PTH is accompanied by increases in cacium excretion in the urine, but this effect may not indicate any specific responses in renal tubular transport of Ca. The primary effect of PTH on Ca metabolism is the result of mobilisation of Ca from bones and enhanced absorption of Ca from the intestinal

tract. As the result of parathyroid gland stimulation, plasma concentration and consequently the filtered load of Ca are increased to an extent that exceeds the tubular reabsorptive capacity for Ca.

RESPIRATORY SYSTEM

Anatomy

Respiratory zone – respiratory bronchioles, alveolar ducts and sacs.

Conducting zone – bronchioles, bronchi.

Conducting zone does not contribute to gas exchange (anatomical dead space): mucus secreting, ciliated cells line conducting zone airways

Airflow to terminal bronchioles by bulk flow

NON RESPIRATORY FUNCTIONS OF THE LUNG

(i) Enhances venous retum

(ii) Heat exchange

(iii) Metabolism – synthesis and catabolism

(iv) Immunological defense

(v) Nose; sense of smell

(vi) Regulates pH by altering the amount of $C0_2$ exhaled

RESPIRATORY MECHANICS

Respiration

Internal respiration – intracellular metabolic processes carried out in the mitochondria. 0_2 is consumed.

External respiration – entire sequence of events involved in the exchange of 0_2 and $C0_2$ between the external environment and the cells of the body.

Ventilation: Exchange of air between the environment and alveoli of the lungs i.e. breathing

Respiratory Cycle

Respiration works by changing the volume of the chest cavity. Before the start of inspiration, respiratory muscle is relaxed. Intravascular pressure = atmospheric pressure and so no air is flowing.

- Atmospheric pressure and so no air is flowing
- At the onset of inspiration, inspiration muscle (diaphragm) contract, which results in enlargement of the thoracic cavity
- As the thoracic cavity enlarges, the lungs are forced to expand to fill the larger cavity
- Because the intraalveolar pressure is less than atmospheric pressure air follows its pressure gradient and flows into the lungs until no further gradient exists.
- Deeper inspirations are accomplished by contracting inspiration muscle more forcefully and by using accessory inspiratory muscle to enlarge the chest cavity.
- At the end of inspirations the inspiratory muscles relax, the chest cavity returns to the original size and the lungs return to the original size.

Respiratory cycles are generally continuous, however during anaesthesia there may be intervals between cycles.

The inspiratory and expiratory phases of the cycles are generally smooth and symmetrical. The horse is however an exception it had 2 phases each during inspiration and expiration.

RESPIRATORY PRESSURES

Air moves from a region of high pressure to low pressure i.e. it flows down a pressure gradient.

Atmospheric (barometric pressure) = pressure exerted by weight of air in atmosphere on objects on earth surface = 760mmHg at sea level.It decreases as attitude increases

Intra alveolar pressure (intrapulmonary pressure) is 760mmHg when equilibrated with atmospheric pressure. Intrapleural pressure (intra thoracic pressure) = 756mmHg

Trans mural pressure = pressure across surface of the lungs – $P_{alveolus} - P_{pleural\ space}$

This trans mural pressure gradient across the lung wall is crucial in expanding the lung to fill the chest cavity.

Although elastic lungs want to collapse, they don't because of the trans mural pressure gradient.

Two forces hold thoracic walls and lungs in close apposition.

(1) Intrapleural fluid cohesiveness (like H_20 between 2 slides)

(2) Transmural pressure gradient (most important)

Pneumothorax – air enters pleural cavity, pressure equalizes with atmospheric pressure, trans mural pressure gradient is gone, lung collapse and thoracic wall springs out.

Pulmonary Elasticity

There is a constraint tendency for the lungs to collapse.

The recoil tendency is due to elastic recoil : returning to pre-inspiratory volume at the end of inspiration

Compliance – measure of distensibility magnitude of change in volume for a given trans mural ΔP.

Normal compliance = 200cm/ml H_20.

Pulmonary elastic behavior depends on

(a) Connective tissue in the lungs

(b) Alveolar surface tension: displayed by thin layers of liquid that lines each alveolus.

Pulmonary surfactant, a complex mixture of lipids and proteins secreted by alveolar cells which reduced alveolar surface tension ↑ pulmonary compliance ↓ reduces lung's tendency to recoil.

Smaller airways are more likely to collapse than the larger ones because of greater surface tension

Laplace law P = 2T/r where P = inward directed collapsing pressure.T = surface tension

AIR FLOW

Flow V = ΔP/R

ΔP=pressure gradient between the atmosphere and alveoli

R is primarily determined by the radius.

Poiseulle's law defines relationship between flow and pressure under laminar flow conditions.

$$V = \frac{\Delta P \pi . r^4}{8.7.\ell}$$

Where ΔP = Pressure drop,V = flow rate,7 = fluid viscosity,L = length of the tube, r = radius of the tube

$$\text{Resistance} = \frac{87\ell}{\pi r^4}$$

Flow can be laminar or turbulent in small airways flow is usually laminar

Laminar flow

(a) Fluid traveling in center moves testes because there is no interference

(b) Fluid in contact with tube wall remains stationary or is slowest due to contract with walls.

(c) Parabolic velocity profile: Fluid velocity decreases with the square of radial distance away from the center of the tube.

(d) Average fluid velocity: In the tube is half of the peak velocity at centre of tube

(e) Pressure difference between two points along the tube is directly proportional to the flow rate $\Delta P=Ki.V$ where

P = Press difference (cmH_20)

K_1 = constant for system (cmH_20sec/ml)

V = flow-rate (ml/sec)

In fully turbulent flow

i) fluid movement occurs both in radial and axial directions

ii) Velocity profile across tube is much blunter than the parabolic profile seen in laminar flow.

iii) because fluid moving in a radial direction can impact on the tube wall, noise is often generated (due to eddy current).

iv) Since energy is consumed in the process of generating the eddies, chaotic fluid movement, a higher driving press is required to support a given flow rate.

v) Pressure difference between two points along the tube increases with the square of the flow rate i.e. doubling the flow rate required more than doubling the driving pressure. $\Delta P \alpha k2.V^2$,ΔP= Pressure difference,K2 = constant,V = flow rate

During tidal breathing:-

- Flow is highly turbulent in trachea
- Less turbulent in small bronchi

- Laminar-like, in the small peripheral airways

Flow (v) is determined by :- Driving press (ΔP),Resistance to flow (R)

Gas exchange

The composition of a gas mixture can be described by the traditional composition or partial pressure.

Air contains 21% oxygen. The oxygen tension of a dry gas mixture is determined by the barometric pressure.

$P0_2$ in dry air at sea level when barometric pressure = 760mmHg is approximately 160mmHg.

During inhalation, air is warmed to body temperature and humidified in the larger air passages.

The $P0_2$ of humidified gas is therefore approximately 149mmHg. i.e $P0_2 = (PB – PH_20) * flO_2$ i.e. $P0_2 = (760\text{-}50) \times 0.21 = 149mmHg$. Where PH_20 in saturated air equals 50mmHg.

Alveolar gas composition is determined by alveolar ventilation and the exchange of 0_2 and $C0_2$.

$PAC0_2$ is determined by the rate of C02 production (V_{C02}) in relation to the amount of alveolar ventilation (V_A).

$PAC0_2 = K.V_{C02}/VA$ where $K = PB – PH_20$

$P0_2$ is lower in the alveolus than in the inspired air because oxygen and $C0_2$ exchange occurs continuously.

The average oxygen tension in the alveoli of the lung can be calculated from the alveolar gas equation.

$PA0_2 = [(PB – PH_20) \times fl0_2] – PA\ C0_2/R$

Where R is the respiratory exchange ratio i.e. the ratio of the rate of $C0_2$ production to that of 0_2 consumption.Alveolar hypoventilation elevates $PAC0_2$ and decrease $PA0_2$.

Alveolar hyperventilation cause a decrease in $PA0_2$because ventilation is increased in relation to carbon dioxide production. Therefore according to the alveolar gas equation as $PAC0_2$ decreases $PA0_2$ increases.

A modified form of the alveolar gas equation can be used to determine $PA0_2$ for clinical purposes as follows.

$PA0_2 = (PB – H_20) \times fl0_2 \times PaC0_2/R$

In this equation, arterial carbon dioxide tension ($PaC0_2$) is substituted for alveolar carbondioxide tension ($PAC0_2$).

Average alveolar $P0_2$ is 100mmHg

Average alveolar $PC0_2$ is 40mmHg

Average arterial $P0_2$ is 100mmHg $PC0_2$ is 40mmHg

Blood entering pulmonary capillaries is systemic venous blood (via pulmonary artery) and systemic venous blood $P0_2$ = 40mmHg $PC0_2$ = 46mmHg

Exchange of 0_2 and C02 between the alveoli and pulmonary capillary blood occurs by diffusion.

The rate of gas movement between the alveolus and the blood ($V0_2$) is determined by the physical properties of the gas (D) the surface area available for diffusion (A), the thickness of the air-blood barrier (x) and the driving pressure gradient of the gas between the alveolus and capillary blood as follows,$V0_2 = D.A. (PA02 – P_{C0P}0_2)/x$

D is the diffusion co-efficient. D is related to solubility and molecular weight.

$D \alpha$ solubility/$MW^{1/2}$.

D for $C0_2$ is 20 x D for 0_2 because $C0_2$ is for more soluble in the body. Faster diffusion rate is offset by $C0_2$ smaller ΔP (6mmHg), compared to 0_2 (60mmHg), so $C0_2$ and 0_2 diffusion more or less equilibrates.

In dissolved lung, 0_2 transfer is more seriously impaired than $C0_2$ transfer because of the difference in D.

In the lung, the barrier separating air and blood is less than 1μm thick. This layer include

(1) Fluid layer lining alveolus containing surfactant

(2) Alveolar epithelium

(3) Epithelial basement membrane

(4) Interstitial space between two basement membrane

(5) Capillary basement membrane

(6) Capillary endothelial cell membrane