Brain & Nervous System

Brain, Neurons, & Axons

- Movement-related Brain Potentials (MRP's)
    - largest MRP's are obtained with forceful contractions performed as rapidly as possible.
- Neurotrophin 3,5, BDNF induce significant increase in the number and length of neurites emerging from spinal cord, the number of motor-endplates per muscle fiber, and the area of innervated muscle fibers.
- these neurotrophins enhance spinal cord motor neuron potential of innervation.
- cocaine blocks dopamine transporters and serotonin
- met amphetamine stimulates dopamine release
- cocaine & amphetamine = increase of dendritic spines on neurons
- aerobic ATP production accounts for 95% of CNS ATP production
- creatine phosphate acts as a carrier of phosphate from production site to site of utilization
-- forelimb motor activity induces cortical angiogenesis
--- over 10 billion neurons in adult brain
--- requires 10% of cardiac output
- 50% of energy resources in nerve cells goes to sodium/potassium pump activity
- 95% of ATP production comes from oxidative metabolism
- oxidative enzyme activity of muscle and neurons can change independently
- glut 1 is the glucose transporter at the blood-brain barrier
- glucose transporters mediate glucose transport into neurons and glial cells
- neurons can live 100 + years....cellular extensions are maintained by continual renewal of protein and lipid whose synthesis takes place in the cell body
- rough endoplasmic recticulum is the synthesis machinery
- vesicles are used to transport things quickly through the axon. Intact mitochondria (axonal mitochondria) are transported anterograde.
- cytoplasm in axon....called axoplasm
- peripheral nerves are served by endoneurial cappillaries.....blood-nerve barrier = the cappillaries and the perineurium
- Group-4 afferent nerve fibers from skeletal muscle.....also called metaboreceptors
    - sense lactic acid concentration in extracellular muscle spaces
- exercise increases vascular density in cerebellum
- there is an electric fish that has neurons that can fire at 800hz – 1250hz [fastest human neuron fires at 300hz]
- rate of which sodium and potassium channels open and rate of which they close…….determines the rate and frequency of depolarization
- rate of sodium & pottasium channel opening and closing is determined by the gene expressed for the channel protein. There are several different genes
- testosterone administration may cause expression of slower channel proteins
- synaptic activity modulates ion currents……..plasticity suggested…create the demand (through training), you get the supply
- Glut-4 is in the central nervous system
- Transforming Growth Factor-beta increases during exercise, causes central fatigue by decreasing motivation for motor behavior….responds to hypoxia/ischemia.

Neurogenesis

- stem cells in the wall of the lateral ventricle give rise to committed neuronal progenitors that migrate to olfactory bulb
- stem cells in the hippocampus go into dentate gyrus
- adult neurogenesis is not restricted to these regions [cerebral cortex, substantia nigra]
- formation and survival of new neurons in the hippocampus can be substantially increased by enriched environment/motor activity
- rate of neurogeneration may exceed rate of stem cell division
- radial glial cells…..progenitors, produce new neurons
- estrogens may maintain or activate radial glial cells
- estrogens are involved in embryonic and adult neurogensis
- estrogens are involved in reparative neurogenesis
- Neddylation....pathway that controls cell cycle and proliferation
    -- neddylation active post-translational modification in the synapse
    -- regulating the maturation, stability and function of dendritic spines.
    -- covalently conjugating Nedd8 to specific targets
    -- Nedd8 conjugation increased during postnatal brain development and is active in mature synapses
    -- neddylation controls spine development during neuronal maturation
    -- neddylation controls spine stability in mature neurons
    -- neddylated PSD-95 was present in spines
    -- neddylation on Lys202 of PSD-95 required for scaffolding protein in spine maturation and synaptic transmission

Neurons

- neuronal adaptations (synaptogenesis) occur with learning and memory
- adaptations occur in motor cortex for motor learning tasks
- adaptations occur in the brain region specific to the nature of the task/information
- spacial memory can be affected by exercise
- electrical synapses are connected by channels called connexons, allowing electrical signals to flow through them
- neuroglial cells (satellite cells) in CNS = oligodendroglia (produce myelin)
- neuroglial cells (satellite cells) in PNS = schwann cells (produce myelin)

- astroglia cells = support neurons by absorbing debri, participate in blood-brain barrier
--- disruption of axonal transport to motor neurons…..causes down-regulation of androgen receptors in motor neurons

Nerve Regeneration
The process = growth at the nerve endings, nerve contact and synapse formation
- IGF's stimulate sprouting of nerve endings
- IGF-1 is a known neurotrophic factor
- peripheral nerves heal by axoplasm regeneration distally to restore nerve tracts
-- A micro-structured, biodegradable, semipermeable hollow nerve guide implant was developed to bridge nerve lesions. Quantitative comparison of cell migration and axonal growth using time lapse video recording in vitro revealed that axons grow eight times faster than neuritotrophic Schwann cells migrate. To accelerate regeneration, purified Schwann cells are best injected into nerve guides before implantation. Nerve guides made from resorbable poly-lactide-co-glycolide support Schwann cell attachment, cell survival, and axonal outgrowth in vitro. The therapeutic concept aims at the development of an `intelligent neuroprosthesis' that first mediates regeneration and then disappears.
- peripheral nerves have plenty of Schwann cells……..thus they can regenerate easily……..peripheral nerves can be used to regenerate CNS nerve fibers
- Schwann cells can be cultured and re-implanted into spinal cord [extracted from ankle area]…… 1 inch of nerve produces 1 meter worth of Schwann cells in 6 weeks
- Schwann cells migrate into spinal cord lession
- cAMP activates Schwann cells…….increases in cAMP increases Schwann cell implantation results….cAMP can be injected
- Sensory neurons turnover every few weeks

Synapses

- early age exposure to “complex” environments (lots of things to explore, see, hear, etc) leads to increased synaptic density at an early age, increases hypocampus neurotransmitters, which facilitates learning later on…adds synapses, dendrites, cappillaries, and glia cells (astrocytes)
- exercise causes some increase in synapses, but less so than motor learning skills (acrobatic motor skills)
- dendrites have all the protein synthesis machinery necessary for protein production
- learning = increase in synapses….adapations are relatively stable (fail to detrain much)
- glia cells do detrain, though synapses are maintained
- astrocyte volume is correlated to synaptic density
- glutamate has metabotrophic effects on dendritic (binds to glutamate receptors) proteins
- synaptic vesicles can reuptake and disengage the membranes in about 10 seconds……in 30 seconds it can release neurotransmitter again…..process called recycling of synaptic vesicles…..a pump puts neurotransmitter back into vesicles

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Sodium-Potassium Pumps (ATPase pumps)
- enzyme composed of 2 polypeptide chains, both have multiple isoforms, and are encoded by separate genes
  - 112 kD alpha subunit (catalytic)..... 3 isoforms (1,2,3)
  - 35 kD beta subunit (glycoprotein)..... 3 isoforms (1,2,3)
- alpa subunit traverses the plasma membrane 6 - 10 times per second
  - contains sites for sodium, potassium, magnesium, ATP, phosphate
- beta subunit spans the plasma membrane
- affinity for different subunits varies by 2 to 3 times, thus various forms of the pump are segregated to different areas
- sodium-potassium channels can translocate up to 10,000,000, ions per second
- maximal rate of sodium-potassium pump ~ 100 per second
- ATPases are limited by the rate of change associated with transitions between inward and outward facing orientation of ion binding sites
- the energy release from the ATP causes the movement of the enzyme and thus the pump action
- the membrane potential affects the rate of pump operation
- rate of pump action is increased by depolarization
- the pump can run backward
- increase in pumping capacity results in an increased power output
- decreased pump activity causes decrease in number of pumps
- dopamine decreases pump activity....dopamine causes and endocytosis of the pumps from the membrane...they get enclosed in endosomes which may act as storage sites thus the pumps may be able to translocate in response to a stimulus
- insulin induces translocation inorder to take up potassium from a meal
- thyroid hormone increases pump activity which increases the number of pumps
- Sodium/Potassium pumps detraining = 2 - 3 weeks
--- The enzyme exists as a heterodimer, consisting of an and a glycosylated subunit. The subunit binds Na+,K+,ATP and cardiac glycosides such as ouabain and is responsible for the ion transport and catalytic properties of the enzyme. The subunit regulates the level of enzyme transported to the plasma membrane, modulates the Na+ and K+ affinity of the subunit and is essential for a stable and functional enzyme .
--- Four (1, 2, 3 and 4) and three (1, 2 and 3) subunit isoforms are known to be expressed in mammalian cells [5, 21 and 31]. Each isoform is encoded by a different gene and has a unique tissue/cell and developmental pattern of expression.
--- The 1 isoform is expressed ubiquitously, the 2 isoform is present predominantly in cardiac, skeletal and smooth muscle and the brain, while the 3 isoform is expressed mainly in the CNS, but is also present in vascular smooth muscle (VSM). In the brain, the 1 subunit is

expressed in both neurons and glia, while the 2 isoform is expressed predominantly in glia and the 3 subunit exists exclusively in neurons. In rodents, the subunit isoforms also differ markedly in their affinity for ouabain.
--- The 2 and 3 subunits have a high affinity (IC50=10-500 nM) and are commonly referred to as the ouabain-sensitive isoforms. The 1 isoform is a ouabain-resistant protein (IC50>10 M).

Ion channels
-- Increased accumulation of reactive oxidative species.....hallmark feature of aging
-- effects of ROS on three major types of ion channels of the central nervous system
- potassium (K+),
- calcium (Ca2+)
- sodium (Na+)
-- 2 mechanisms through which ROS affect ion channels
----- direct oxidation of specific residues
----- indirect interference of pathways that regulate the channels
-- interaction of ion channels with ROS is pervasive in the central nervous system and likely constitutes a general mechanism of aging

myelin
- lipid rich myelin
- sodium channels are clustered at the nodes of Ranvier
- myelin covers and masks internodal parts of the axon which contain fewer sodium channels and higher density of potassium channels
- Mechanical trauma to the spinal cord produces axonal destruction, extensive demyelination by damaging oligodendrocytes and astrocytes. Axons that survive injury lose their myelin sheath. Loss of the myelin sheath causes reduced conduction velocity or overt nerve conduction block that play a role in the neurological deficits after spinal cord injury. Functional recovery depends on nervous system remyelinating ability.
-- In the mature brain, the highest cholesterol content is found in myelin.
-- Cholesterol in the brain is a risk factor for certain neurodegenerative diseases
-- ability to synthesize cholesterol in myelin-forming oligodendrocytes.
-- inability to synthesize cholesterol = CNS myelination severely perturbed∑∑..ataxia and tremor.
-- cholesterol is an indispensable component of myelin membranes and that cholesterol availability in oligodendrocytes is a rate-limiting factor for brain maturation.

-- nuclear zinc-finger protein Zeb2 (Sip1) is essential for Schwann cell differentiation and myelin synthesis
-- ince Zeb2-deficient Schwann cells continuously express repressors of lineage progression, 'inhibiting the inhibitors' emerges as a new principle
-- transcriptional regulator Zeb2
----- required for the onset of peripheral myelination and remyelination
----- recruits HDAC1–HDAC2–NuRD co-repressor complexes to antagonize inhibitory effectors
----- activate promyelinogenic factors
-- Mowat-Wilson syndrome–associated ZEB2 mutation
----- disrupts HDAC–NuRD interaction, abolishes Zeb2 activity for Schwann cell differentiation
-- myelin is synthesized as a multilamellar membrane
-- myelin pieces are gradually released from aging myelin sheaths and are subsequently cleared by microglia
-- myelin fragmentation increases with age and lead to the formation of insoluble lipofuscin-like lysosomal inclusions in microglia
-- age-related myelin fragmentation is substantial....leading to lysosomal storage and contributing to microglial senescence and immune dysfunction

Muscarinic receptors

- neurotransmitter binds to receptor……
--- causes 2nd messenger [GTP] to be released inside cell.
--- which causes slow acting, long term changes as compared to sodium channel activation

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Astrocytes
- glia cells, the most abundant of all glial cells
-- responsible for regulating extracellular levels of glutamate and potassium during neuronal activity
-- glutamate clearance is handled by glutamate transporter
--- glutamate transporter 1
--- glutamate–aspartate transporter

Microglia

- microglial cells function as brain macrophages
- cortisol decreases microglial cell production of NO by inhibiting production of nitric oxide synthase
- catecholimines inhibit NO production, causes decreased immune function of microglial cells
- there are “Terminal Schwann cells” at neuromuscular junctions that encapsulate the nerve terminal
    -- helps re-attach severed nerve terminals to a junctoino
- Astrocytes are CNS glial cells…….Terminal Schwann Cells are PNS glial cells
-- regulate adult neurogenesis via signaling molecules following enlargement of microglia, release of cytokines
-- microglia and other immune-reactive cells in the brain can support or disrupt neural processes
-- inflammatory microglia, reduce cell proliferation, cell survival, and cell function of new neurons
-- protective microglia support adult neurogenesis
-- some cognitive deficits associated with inflammation may in part be related to inflammation-induced reductions in adult hippocampal neurogenesis
-- cerebellar and hippocampal microglia....exist in a more immune-vigilant state.
-- loss of microglia.....key features during aging
-- loss of microglia.....feature of brain degenerative diseases including Alzheimer's
-- phagocytic cells crucial to the process of healthy brain development.
-- contribute to the patterning of the developing central nervous system by regulating programmed cell death
-- contribute to the wiring of the developing central nervous system by regulating synapse pruning and maturation.
-- important in the pathology of neurodevelopmental disorders
-- chronically activated microglia promote non-amyloid Alzheimer's disease pathology

-- the primary cells that exert immune function in the central nervous system
-- microglia act as key players in the initiation of neurodegenerative diseases
-- microglia have functional plasticity and dual phenotypes
    ——— proinflammatory M1
    ——— anti-inflammatory M2
-- inhibiting the M1 phenotype while stimulating the M2 phenotype has been suggested as a potential therapeutic approach for the treatment of neuroinflammation-related diseases
-- resveratrol
    ——— demonstrated to exert anti-inflammatory effects by suppressing M1
    ——— reduced inflammatory damage
    ——— promoted microglia polarization to the M2 phenotype
    ——— overexpression of PGC-1α by resveratrol could be a potential therapeutic approach to suppress neuroinflammation by regulating microglia polarization

Oligodendrocyte progenitor cells
-- comprise about 5% of the CNS cellular content.
-- continuously renewed with rates increasing during pathologies.
-- can modulate neuronal activity, myelination
-- are recruited to injury sites.
-- contribute to the immune response and the formation of the glial scar

NG2-glia
-- express the chondroitin sulfate proteoglycan NG2
-- during development eferred to as embryonic oligodendrocyte precursors
-- in the adult CNS.....eferred to as adult NG2-glia
-- they give rise to myelinating oligodendrocytes at all times of life
-- transcription and epigenetic marks is essential for oligodendrocyte progenitor cell proliferation and differentiation
-- transcriptional repression and activation.....dysregulation of these epigenetic events may affect demyelinating disorders
    ----- epigenetic regulation includes DNA methylation, chromatin and non-coding RNA changes.
    ----- epigenetic changes of nuclear structural components define transitions in NG2 cells.
    ----- epigenetic dysregulation can result in defective myelin repair or gliomas formation.

Connexins (Cx)
— expressed in glial cells
— tumor suppressive action via downregulation of IGF-1 receptors in gliomas
— Connexin 30 impedes migration, invasion and colony formation of glioma cells
— in brain…crucial role in cell communication though regulation of cell growth and proliferation
— inhibits IGF-1 in glioma

nerve fibers...sympathetic nervous system
-- innervate bone marrow

-- regulate hematopoietic progenitor cells
-- stress impacts acute lymphoblastic leukemia

peripheral sensory neurons
-- neurons divided into three functional classes
    -- nociceptors/pruritoceptors
    -- mechanoreceptors
    -- proprioceptor
-- distinguished expression of TrkA, TrkB or TrkC receptors, respectively

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Pituitary
-- presence of dendritic cells in the pituitary gland
    ----- a role in communicating immune activation to the hypothalamic pituitary adrenal axis
-- presence of CD11c/eyfp+ cells throughout the pituitary
    ----- non-lymphoid dendritic cells
-- pro-inflammatory cytokine production by dendritic cells within the pituitary may activate the release of glucocorticoids from the adrenals via ACTH
-- resident dendritic cell population of the pituitary gland coordinates glucocorticoid release

Thyroid
-- 50% of autopsies found thyroid nodules
    --- JAMA March 3, 2015....detection of asymptomatic thyroid nodules has increased
    --- among patients with asymptomatic, sonographically or cytologically benign thyroid nodules
    --- majority of nodules....no significant size increase during 5 year follow-up and thyroid cancer was rare
-- hyperthyroid
    --- L-carnitine is a peripheral antagonist of thyroid hormone action. It inhibits the entry of triiodo thyronine and thyroxine into the cell nuclei. Through a randomized trial, Benvenga et al. showed that 2–4 g of oral L-carnitine per day could reverse hyperthyroid symptoms even in the most serious form of hyperthyroidism: thyroid storm. They suggest that since hyperthyroidism impoverishes the tissue deposits of carnitine, there is a rationale for using L-carnitine at least in certain clinical settings. Incidentally, the fact that carnitine failed to prevent relapses of hyperthyroidism further supports the concept that carnitine action is in the periphery and not in the thyroid gland
-- T3 is active form...causes thyroid gland to produce thyroid hormone
    ---- binds to nuclear receptors on nuclear membrane
-- there is T3 and Reverse T3
-- reverse T3 is only slightly active
-- T4 is inactive form....is in this form during transport through the blood
-- for T4 production, need iodine....T4 is 4 molecules of iodine
    ----- conversion of T4 to T3....done by enzyme
-- TSH is comprised of protein, magnesium, zinc, B vitamin
-- for iodine transport into the thyroid requires vitamin C

Thyroid Hormone
- T4 is 4 iodine atoms
- T3 is 3 iodine atoms
- increases neurotrophins
- can cause proliferation of T lymphocytes
- can alter lymphocyte reactivity

Hypothalamus
- ventral medial nucleus of the hypothalamus decreases immune cell activity by sympathetic nerves (norepinephrine) that enter the spleen.....lymphocyte activity can be decreased by norepinephrine
- ventral medial hypothalumus controls liver glycogen
- the retino-hypothalmic nerve tract going from the eyes to the super-chiasmatic nucleus of the hypothalamus uses serotonin as it's neurotransmitter....serotonin agonists cause phase shifts in the circadian release of melatonin, similar to light exposures
- sleep promoting neurons in the hypothalamus [ventrolateral preoptic nucleus] send inhibitory signals to midbrain neuorns that promote wakefulness

Sub-Thalmic Nucleus (STN)

Ventral tegmental area (VTA)

- has dopamine projections to nucleus accumbens
- has projections [perhaps glutamate] to prefrontal cortex
--- site of origin of the mesolimbic system
--- majority of cell bodies in this region are dopaminergic
--- axon terminals release dopamine in target areas [nucleus accumbens and prefrontal cortex]
--- in the VTA….glutamatergic processes via N-methyl--aspartate (NMDA) receptor/channel activity regulate dopamine cell excitability and dopamine release
--- Activation of the NMDA receptor/channel increases burst firing in VTA dopamine neurons
--- glutamatergic stimulation of the VTA or ventral subiculum induces dopamine release in the VTA coincident with motor activity
--- deficits in NMDA receptor function have been implicated in schizophrenia, Alzheimer's disease, AIDs dementia/complex, among other CNS disorders
--- IL-2 modulates the excitability of VTA neurons via NMDA receptor/channel

Pineal Gland
- neuronal input is norepinephrine
- neuronal output is melatonin

Nucleus Accumbens
-- dopamine enriched site where incoming cortical and limbic system signals are integrated and translated for expression of emotional, motivational, and adaptational behaviors. It receives excitory amino acid afferents form the prefrontal cortex (subiculum, amygdala, thalmic nuclei).
- dopamine in hypothalamus (nucleus accumbens).....related to speed of animals
- dorsal striatum……..location of parkinsons problems
- ventral striatum……location of addiction problems

Substantia Nigra

- changes in glucose levels in substantia Nigra [SN] causes changes in Dopamine release. Dopamine has increased release with low glucose, and decreased release with high glucose. Glucose responsive neurons increase firing rate when glucose levels increase. It is modulated by an ATP sensitive potassium channel. Glucose inactivates the channel, which leads to increased depolarization [increase firing].

Frontal Cortex
- frontal cortex is thicker with exposure to enriched environments
- left frontal opercular region, for speech articulation
- insula of left hemisphere (an island of cortex deep to the frontal and temporal lobes....used in speech articulation

Prefrontal Cortex
- is the place most affected by serotonin dysfunction in depression...in depression serotonin input is abnormal in this area
- major area of mood regulation, behavior inhibition
- glutamatergic neurons synapse with basal ganglia neurons
- has glutamate projections to nucleus accumbens
- has dopamine projections to VTA
- modulates dopaminergic activity in the nucleus accumbens
- disruption of prefrontal cortex dopamine may cause long term attention/memory decrease
- place where the command to produce a motor behavior originates

Medial Pre-optic Area [MPOA]

- controls sexual behavior……has dopaminergic input/output
- dopamine affects sexual behavior

Visual Cortex

- neurons respond to one eye or the other [have eye specific neurons]
- lateral connections to other neurons is critical to the organization of the visual system
- light…to…retina….to…photoreceptors…to….optic nerve…..to….neuron….to….lateral connections….to other neurons

Insular Cortex
- has immunomodulatory ability involved in visceral reactions and stress, also called gustatory or visceral cortex because it receives gustatory and visceral information from the thalamus.

Cerebellum
The denate nucleus of the cerebellum is strongly activated during sensory tasks. The cerebellum may act to influence the motor system such that sensory receptors are placed in the best position to acquire high quality sensory information. Cerebellum may be for sensory acquisition and discrimination rather than movement.

Medulla

- dorsal horn of medulla processes nociceptive and thermo-sensory information, has opiod receptors in abundance, can inhibit nociceptive transmittion.
- parts of the ventral medial medulla are responsible for modulation of the sensitivity to pain at the level of the spinal cord, by way of opiod receptors

hippocampus

The subiculum is an important structure with respect to hippocampal output and may play an important role in cognitive function. Activation of serotonin receptors in subiculum reduces response amplitudes in the CA1 region of the hippocampus. Glutamenergic transmission plays a major role in plasticity phenomena. Serotonin receptor activity suppresses subicular transmission at low but not high frequencies.
- glucocorticoids alter antioxidant enzyme capacity
- levels of superoxide dismutase and glutathione peroxidase are decreased in the presence of glucocorticoids
-- in brain, hippocampus affected most
- dividing progenitor cells in the dentate gyrus allow for production of new neurons throughout life
- new born neurons generated from these progenitor cells migrate, differentiate, and extend axons.
- episodic memory
- special memory = posterior hippocampus
- hippocampus works with Dintate Gyrus
- hippo has estrogen receptors located on inhibitory interneurons…….estrogen increases synaptogenesis
- estrogens affect 4eBP1 for synaptogenesis

Limbic System

- sexual behavior……limbic activity drives sexual behavior
--- amygdala, medial pre-optic area [dopaminergic activity], ventral medial nucleus of hypothalamus

Basal Ganglia
- Sub-Thalmic Nucleus (STN)...reguarded as the most important control structures of the basal ganglia
- neurons in the STN become pathologically overactive in Parkinson's disease. These neurons use glutamate.
- GABA = 95% of neuronal output types in this area…….the rest =
--- cholinergic interneurons……dopaminergic……glutaminergic

Amygdala
- verbal and non-verbal expressions of fear and anger are interpreted by the amygdala
- stress causes serotonin production in amygdala
- storage of "fear conditioning" information
- some areas cause extinction of conditioned fear behavior
- prefrontal cortex can override fear conditioned behavior
-- active in perception and processing of emotional experiences [fearful, aversive oriented experiences]
-- modulates hippocampus during storage of emotional memories related to fearful, aversive experiences

Medulla Oblongata
- controls electric discharge in electric fish

nucleus tractus solitarius (NTS)
--- central terminus for baroreceptor and chemoreceptor afferents.
--- regulate central cardiovascular function.
--- NTS has also been shown to possess high levels of estrogen receptors (ERs)
--- Estrogen causes decrease in glutamate activity…….causes decrease in sympathetic tone in cardiovascular system
--- estrogen inhibits glutamate induced NTS neuronal activity through estrogen's activation of estrogen receptors in the NTS

Cerebral Spinal Fluid
-- normal cerebral spinal fluid production rate in an adult.....
--- 0.35 ml per minute
--- 20 ml per hour
--- 500 ml per 24 hours
-- capacity of normal lateral and third ventricles is approximately 20 ml
-- total cerebral spinal fluid volume in an adult is 120–150 ml
-- in normal circumstances cerebral spinal fluid is recycled over three times each day

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Nitric Oxide

- Nitric oxide (NO) is a biological messenger, formed fro arginine by 3 nitric oxide synthases (NOS)
- nitric oxide synthase has a binding site for nitric oxide
- other substances (arginine analogs) can compete for the binding site, thus inhibiting NO production
- arginine analogs = nitro arginine monomethyl ester (NMME), nitro arginine methyl ester (NAME)
- Nitric oxide is short lived
- NO synthesis occurs with microbial infections…..causes decreased immune function via oxidative damage….impairs release of gamma interferon. NO Synthase is increased for long periods during an infection. Allows production of nitrogen oxide species [peroxynitrite = not superoxide]. NO induced oxidative stress allows virus evolution.
- NO is produced by macrophages
- has microbial and cytotoxic activities
- made from l-arginine….catalysed by nitric oxide synthase [NOS]
- 3 forms of NOS
    --- endothelial cell NOS….[dependent on elevation of calcium]
    --- neuronal cell NOS……[dependent on elevation of calcium]
    --- inducible NOS
- adrenaline inhibits macrophage NO production
- brain endothelial NO cause vasodialation
- catecholimines inhibit NO production, causes decreased immune function of microglial cells
- cortisol decreases microglial cell production of NO by inhibiting production of nitric oxide synthase
- glutamate can cause NO related oxidative damage

Dopamine & Dopaminergic Neurons

- decreased dopamine output may lead to increased glucocorticoid production
- dopaminergic neurons have glucocorticoid receptors
- implicated in reinforcing and motivating behaviors, as well as movement
- in hypothalamus (nucleus accumbens).....related to speed of animals
- in hypothalamus (caudate nucleus).....related to posture of animals
- brain levels can be significantly decreased by serotonin
- during exercise...at exhaustion, dopamine in midbrain area is decreased substantially while being the same in other areas. Everything is region specific.
- exercise can reverse “age-related” declines in dopamine function
- exercise increases dopamine receptor density
- people who are detached, cold, alloof, have decreased D2 receptor density
- post-synaptic to dopaminergic input = prodynorphin, proenkephalin
- Immune cells have opiate receptors which affect their function. Relaxation may increase immunocompetence via opiates.
- tyrosine 3’ hydroxylase converts tyrosine into L-DOPA…..is the rate limiting enzyme for dopamine produciton
- one of the side effects of prozac [nervousness, anxiety, restlessness] due to the effects of decreased dopaminergic neurons
- changes in glucose levels in substantia Nigra [SN] causes changes in Dopamine release. Dopamine has increased release with low glucose, and decreased release with high glucose. Glucose responsive neurons increase firing rate when glucose levels increase. It is modulated by an ATP sensitive potassium channel. Glucose inactivates the channel, which leads to increased depolarization [increase firing].

-- dopamine neurons may play an important role in the behavioral changes associated with chronic social stress during puberty.
--- Dopamine (DA) of hypothalamic origin exerts tonic inhibitory control over prolactin (PRL) secretion…… a significant reduction in PRL levels was detected after stress compared to non-stressed

Glutamate

- glutamate stimulation of glucose uptake occurs in the same range of concentrations as those necessary to cause neuronal death.
- excessive exposure to glutamate causes massive neuronal degeneration.
- glutamate causes accumulation of intracellular calcium through an influx from NMDA receptors and from intracellular stores. This is the primary cause of neuronal death.

-- After glutamate release, specific transporter proteins rapidly remove extracellular glutamate from the synaptic cleft.
-- The clearance of excess extracellular glutamate prevents accumulation under normal conditions;
-- CNS injury elevates extracellular glutamate concentrations to neurotoxic levels.
-- steroid hormones affect glutamate receptor abundance……decrease in steroid hormones = decrease in glutamate receptors

-- Glutamate transporters….

-- (EAAT1)
-- (EAAT2)
-- (EAAT3)
-- (EAAT4)
-- (EAAT5)

-- neuronal glutamate transporter
-- EAAC1
-- (EAAT3)

-- upregulation of transporters following injury occurs rapidly
-- extracellular calcium important for the mechanism of glutamate re-uptake
-- glutamate increases glutathione production
-- in aged animals…an increased mGlu2/3 receptor protein expression was found in the frontal cortex, thalamus, hippocampus and corpus callosum.

tryptophan
-- 2 pathways.....immune system, brain
-- stress, overtraining sends preferentially to immune system....that reduces levels to brain.....result in sleep disturbance, mild depression, etc

serotonin
-- 40 to 60% reduction in receptors with the use of anti-depressants
Serotonin reuptake inhibitors work on the serotonin transporter. The transporter inactivates released serotonin by taking it from the extracellular space, back into the nerve terminal. Serontonergic neurons are located mainly in the raphe nuclei of the brain stem. Ascending pathways go into the hippocampus, cerebral cortex, and other areas that participate in affect around the midbrain. Glucocorticoids can downregulate serotonin transporter gene expression especially in aged people. This would make the use of serotonin reuptake inhibitors less effective in depressed patients, especially in ederly depressed patients. Also, transporter function may be changed, with no change in transporter number, in young patients.
- serotenergic neurons synthesize mono-amine oxidase-B exclusively....degrades dopamine
- noradrenergic neurons synthesize mono-amine oxidase-A.....deaminates serotonin
- cortisol downregulates serotonin receptors
- Serotonin inhibits feeding behavior by affecting serotonin receptors (5HT2a) on the paraventricular nucleus (PVN) on the hypothalamus.
- Serotonin is a powerful anorectic agent
- 5HT2c receptor.....associated with anorectic effects
- mutation of 5-HT2c can cause hyperphasia and obescity
- Blockade of serotonin synthesis induces hyperphagia. Antenuates NPY induced hyperphagia by activation of corticotropin releasing factor.
- There are brain areas where presynaptic serotonin receptors control the release of glutamate.
- Descending serotonergic pathways projecting to the spinal cord are known to be activated by and to modulate sensory information, both non-nociceptive as well as nociceptive through 5-HT 1a receptors. These receptors are mainly located presynaptically on the primary afferents.
- Tryptophan hydroxylase (TPH) is the rate-limiting enzyme of serotonin synthesis
    - first enzyme in the pathway converting tryptophan into melatonin
    - controled by circadian function
- serotonin decreases cerebral spinal fluid production by affectiong sodium-potassium pumps.....serotonin decreases pump activity thus there is a decrease in sodium transport which causes a decrease in cerebral spinal fluid production

N-methyl-D-aspartate [NMDA recptors]

- receptor for excitory amino acids [ie. Glutamate, aspartate]

GABA
- inhibitory, opposite of excitory [ie glutamate]
- trine [amino acid] is a precursor for GABA

GABA receptors [gamma-aminobutyric acid]
- one of the most prominent modulators of GnRH neurons
- stimulates and inhibits secretion of GnRH from the hypothalamus
- estrogen increase GABA and glutamate in hypothalamus
- progesterone decreases GABA and glutamate in hypothalamus
- comprised of 5 subunits
- has receptors for alcohol, anesthetics, valium
- glycine receptors are the main inhibitory receptor in spinal cord…….GABA is main one in the brain

Resolvins
- - resolvins.....resolution-phase interaction products [first encountered in resolving inflammatory exudates]
- compounds made by the body from omega-3 fatty acids
- produced by the COX-2 pathway
- reduce cellular inflammation by inhibiting the production and transportation of inflammatory cells and chemicals to sites of inflammation
- derived from EPA are designated as resolvins of the E series
- from the precursor DHA are denoted as either resolvins or protectins ('neuroprotectins') of the D series

Protectins
-resolvin formation in brain tissue
- Synthesis of NPD1 is induced as a response to oxidative stress and/or activation of neurotrophins
- (N)PD1 has anti-inflammatory effects
- protects retinal epithelial cells from apoptosis induced by oxidative stress.
- promotes apoptosis of T cells
- has beneficial effects on asthma

Kynurenine (KYN)

- cytokine-stimulated production of kynurenine from tryptophan
- increases in cerebrospinal fluid are associated with depressive symptoms secondary to immune activation
- may alter dopaminergic and glutamatergic tone, contributing to increased arousal, agitation and impulsivity

Neuropeptide Y
-- 36 amino acid appetite regulator
-- isoforms, Y1, Y2, Y3, Y4 , Y5
-- one of the most potent appetite stimulators in the brain
-- produced by adipocytes
-- production stimulated by insulin
-- adipocyte derived NPY affects lepton production
-- peripheral functions.....regulation of angiogenesis, vasoconstriction,
-- causes up regulation of lipoprotein lipase (lipogenesis)

Motoneuronotrophic factor (MNTF)
- endogenous neurotrophin specific for the human nervous system
- effects of MNTF.....motoneuron differentiation, maintenance, survival, and reinnervation of muscles and organs
- a neuro-signaling molecule, binds to specific receptors

α-Synuclein
-- protein helps dilate the fusion pore during vesicle exocytosis, promoting release of certain neurotransmitters
-- present at high levels in all neurons and their synapses

Kynurenic Acid
An endogenous antagonist to glutamate receptors. It is neuroprotective. Synthesized predominantly in astrocytes from the precursor...kynurenine.

Connections
Substance P and sustance K are secreted by afferent sensory-nerve terminals. They stimulate immunocompetent cells to secrete inflammatory cytokines. The immune system can interact with
sensory-nerve endings to inhibit pain. The opiod receptors on peripheral sensory nerves are up-regulated during inflamation. Endogenous substances such as corticotropin releasing hormone and cytokines can stimulate the release of opiod peptides which produce local analgesia. Suppression of immune system abolishes these effects. Immune cells may be able to produce opiods that bind to sensory nerves and cause analgesia by inhibiting excitability or the release of excitatory/proinflammatory neuropeptides. Three types of opiod receptors mu, delta, kappa. Opiods increase potassium currents and decrease calcium currents in the cell bodies of sensory neurons, both of which can inhibit neuronal firing. Opiods inhibit the calcium dependent release of excitatory/proinflammatory compounds (ie. substance P) from peripheral nerve endings which may contribute to the anti-inflammatory actions of opiods. Post exercise-meditation modifies the suppressive effect of strenous physical stress has on the immune system.

Melatonin, Circadian rythms, & Sleep
- receptors located on CD4's, none on B-lymphocytes
Advancing (eastward jet lag) sleep/circadian cycles.....the overall advance of melatonin profiles is primarily achieved during the initial exposure to a period of darkness. Exposure to dark affects the circadian phase. Melatonin secretion is not affected by daytime sleep.
- The suprachiasmatic nucleus (SCN) is the pace maker of the circadian timing system.
- Reduce bright light exposure at least 2 hours prior to regular bed time.
- Light at nite has an acute suppressive effect on pineal gland synthesis of melatonin.
- Suppression is proportional to the intensity of light exposure, but not duration.
- Exposure to light at nihgt inhibits melatonin secretion in a dose dependent manner. The brighter the light, the greater the decrease in plasma melatonin concentrations.
- The duration of melatonin secretion depends on the duration of darkness, so that 24 hour melatonin secretion is greater during the winter than during the summer.
- Descending serotonergic pathways may affect sleep and waking by dampening ascending sensory information, possibly precipitating sleep.
- Bright light exposure early in the morning results in phase advances of wake/sleep rhythms. There are highaffinity receptores for melatonin in the hypothalamic suprachiasmatic nucleus, the main circadian pacemaker.
- Both light and melatonin are able to affect the oscillatory function of the circadian clock. Light has a direct inhibitory influence on the melatonin formation during the period of the abudant systhesis.
- The direct suppressing effect of light on the melatonin formation during the dark period might be one of the factors resetting the phase of the pacemaker.
- Light exposure is a stronger regulator of melatonin release than is administration of melatonin it self. A single light exposure at night is able to shift the circadian rhythms.
- Maintenaning high melatonin levels via administration, during light exposure, fails to counteract the light induced decrease in melatonin synthesis.
- the retino-hypothalmic nerve tract going from the eyes to the super-chiasmatic nucleus of the hypothalamus uses serotonin as it's neurotransmitter....serotonin agonists cause phase shifts in the circadian release of melatonin, similar to light exposures
- 200mg of caffeine at night decreases melatonin....mechanism of sleep affects of caffeine
- the major daily growth hormone surge occurs during non-rapid eye movement sleep. The inhibition of growth hormone releasing hormone, decreases during sleep

Effects of Sleep on Adaptations to training
Sleep is a period for neurological regeneration and immune system stimulation. Melatonin functions as a hormone outside the brain. It stimulates T-lymphocytes in the periphery. Sleep is a time that the nervous system uses to detoxify itself using glutathione. Glutathione is oxidized and becomes a sleep promoting substance. The oxidized glutathione (GSSG) shuts down excitory amino acids, allowing neurons to engage in repair. The quality of sleep is of greater importance than the length of sleep.
- alertness decreases between 2 - 5pm and 2 - 5am
- (15 - 45 minute) nap after lunch increases alertness
- melatonin stimulates the antioxidant enzym glutathione peroxidase
- melatonin inhibits nitric oxide synthase from generating more free radicals

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Neurotrophins

- regulation of neurotrophin release is linked to neuronal activity
- glucocorticoids and stress have inhibitory effects on neurotrophins
- neurotrophins regulate neuronal connectivity in the central nervous system
- aid in maintenance of neuronal function
- prevent process of apoptosis
- all of them bind to the p75 receptor
- all of them bind to the receptor for tyrosine kinases (Trk)
    - NGF binds to Trk-A
    - NT 4/5 & BNDF bind to Trk-B
    - NT 3 binds to Trk-C
- impact synaptic efficacy
- glucocorticoids downregulate neurotrophin mRNA

Ciliary Neurotrophic Factor (CNTF)

Brain Derived Neurotrophic Factor (BNDF)
- activates glutathione
- exercise increases BNDF gene expression
- an immunomodulator that controls macrophages
- supports maintenance of function of dopaminergic neurons
- regulated by light, and exercise
- regulates expression of somatostatin in the CNS
- BNDF critical to learning and memory…….increase synaptic activity, facilitates postsynaptic action potentials and the frequency of them…..increases NMDA responsiveness
-- BDNF increases nuclear androgen receptors in motor neurons……in the presence of testosterone

Glial cell Derived Neurotrophic Factor (GDNF)
- GDNF is highly specific neurotrophic factor for dopaminergic and developing neurons
- estrogen is a cofactor in the actions of nerve growth factors

Nerve Growth Factor (NGF)
- NGF protects neurons against excitotoxicity by stabilizing intracellular calcium
- activates glutathione
- exercise increases NGF gene expression
- role in synaptic connectivity.....influencing growth of neuronal processes
- affects neuron soma size and dendrite complexity

Fibroblast Growth Factor (FGF)
- mediates glial cell modulation of neuronal function
- has trophic effects
- T-cells can affect production of FGF
    - IL-4 enhances FGF production
    - gamma-Interferon decreases FGF production
- mediates glial cell modulation f neuronal function.....has trophic effects

Transforming Growth Factor-beta [TGF-beta]

- Transforming Growth Factor-beta increases during exercise, causes central fatigue by decreasing motivation for motor behavior….responds to hypoxia/ischemia.

Beta-endorphin
- regulates Natural Killer cell activity (enhancement)
- mainly sythesized in cells located in the arcuate nucleus (ARC) of the medio-basal hypothalamus
- derived from proopiomelanaocortin (POMC).
- Glucocorticoid receptor steroid complex can bind to DNA of POMC, inhibiting POMC transcription.
- Major B-endorphin tracts project to the periaqueductal gray of the mid-brain, the site of pivotal importance for regulation of nociception.
- Glutamate may increase beta-endorphin secretion.
- - 750mg of D-Phenylalamine increases endorphin levels by decreasing their enzymatic breakdown

Methionine-enkaphalin
- regulates Natural Killer cell activity (enhancement)

Glucocorticoids (GC)

- 2 sub-classes of corticosteriod receptors
  -- type 1 = mineralcorticoid receptor
  -- type 2 = glucocorticoid receptor (more abundant, especially in immune cells)
- Stress = release of corticotrophin releasing hormone --adrenocorticotrophic hormone (ACTH) -- glucocorticoids.
- Neuropeptide Y modulates immune responses. NPY inhibits natural killer cell activity. NPY may be produced in increased amounts from stress.
- lymphocyte activity can be decreased by norepinephrine
- high GC levels decreases glucose uptake in neurons
- glucocorticoids accascerbate neuronal aging
- brain regions have differing amounts of corticosteroid receptors
- glucocorticoids increase the toxicity of ROS generators, and increase the level of ROS produced in cells
- glucocorticoids alter antioxidant enzyme capacity
- levels of superoxide dismutase and glutathione peroxidase are decreased in the presence of glucocorticoids
  -- in brain, hippocampus affected most
- Stress = increase glucocorticoids -- increases tryptophan hydroxylase = increased serotonin
- Stress = increased lipolysis -- increased free tryptophan = increased serotonin
- Removal of tryptophan from the diet lowers mood in humans and reverses the positive effect of antidepressive drugs in depressed patients.
- Depression is associated w/hypercortisolemia and decreased serotonin transmission, while Chronic Fatigue Syndrome is associated with hypocortisolemia and increased serotonin transmission.
- cortisol downregulates serotonin receptors
- corticosteroids cause avascular necrosis of bone along joint surfaces
- cortisol can impair macrophage funciton, increase foam cell formation in artery wall, accelerating atherosclerosis
- Effects of Glucocoticoids (cortisol,etc) on Translation…….. causes dephosphorylation of 4E-BP1
- glucocorticoids suppress Growth Hormone, IGF-1 production, and expression of GH and IGF-1 receptors
- RU486 is a blocker of glucocorticoid receptors

Corticosteroid Binding Globulin (CBG)
modulates access of cortisol to various tissues. Only non-CBG bound cortisol can diffuse into cells and bind to intracellular corticosteroid receptors. CBG is downregulated during chronic stress, thus CBG rather than solely elevated cortisol levels, can be a mechanism of decreased immune activity in chronically stressed individuals.

Binding Globulin
- may bind testosterone
- binds cortisol…..Cortisol binding globulin [CBG]
- neurotphils produce substance that causes CBG to release cortisol…..causes increase in local cortisol levels
- growth hormone may decrease CBG
- CBG made in liver
- CBG levels and increase and decrease…….chronic stress decreases CBG
- there may be CBG receptor sits on cell membranes…..binding to cell membrane may cause release of cortisol [may occur in prostate cancer]

Prolactin
- stress hormone produced by pituitary

Corticotropin Releasing Hormone [CRH]

- feeding decreases CRH release

Neuroglobin

--- 151 amino acids….hemo-protein that binds oxygen, acts like myoglobin

Brain glycogen
main glycogen stores are in astrocytes
Astrocytes send glucose to neurons
- of all cells in the brain, neurons use most of the energy
- glycogen levels are 3 to 4 times higher than the amount of brain blood
-have about 3 to 5 days of glycogen stores
- Glut 1 functions at blood-brain barrier

Exercise
- exercise increases hippocampus BDNF [brain derived neurotrophic factor]
- exercise induces hippocampus synaptic plasticity and expression of molecules implicated in learning and memory
- exercise regulates properties of synaptic transmission under the direction of BDNF
- exercise increases levels of synapsin 1 and synaptophysin
- brain macrophages can contribute to the increase in brain IL-1β and fatigue associated with exercise-induced muscle damage.

Brain Impact on Training Adaptations
Growth factors released into blood impact transcription factors in muscle. Thyroxin can impact gene expression. Insulin impacts transcription and translation. Insulin affects translation by increasing amino acid transport to the intra-cellular pool, thus enhancing tRNA access to necessary amino acids. Steroid hormones cross the membrane, bind to receptor in nucleus, and activates acceptor protein that acts as a transcription factor by attaching to enhancer sequences on DNA. Locally produced IGF-1 may act in this manner. Exercise induced anabolic effects of physical activity might be at least partially mediated by an increased production of muscle IGF-1 that appears to be independent of growth hormone. IGF-1 increases protein synthesis. Autogenics/meditation impacts immune cells by way of cortisol decrease. Cortisol decrease causes increase in testosterone to cortisol ratio and reduced downregulation of transcription/translation. All cells in the body have receptors for neuropeptides, thus fitness levels can be impacted by our thoughts. Stress hormone (cortisol) levels increase following a workout and compete with testosterone for binding to receptors on muscle fiber membranes and other tissues. Testosterone can improve adaptations to the training stimulus, and cortisol can decrease adaptations. Thus the ratio of testosterone to cortisol can have a significant impact on fitness improvement over the course of a training year, by impacting each workout that is completed. Autogenic relaxation or meditation completed immediately following a workout has been shown to reduce cortisol levels and increase the testosterone to cortisol ratio, leading to favorable effects on training adaptations. The relaxation and meditation following a workout also has favorable effects on the immune system, improving the ability of cells such as lymphocytes to respond during the recovery period.

Migraine Headache

- symptoms decrease with serotonin agonist
-- corticotropin-releasing hormone (CRH), known to precipitate or exacerbate migraines

Chronic Fatigue, Fibro-myalgia, depression, pre-schizophrenia all share the following symptoms as the process progresses through toward deeper stages of brain cell deficits.....
-- difficulties concentrating
-- loss of energy
-- disturbances in perception
-- suspiciousness, depression, anger
-- emergence of odd beliefs

Chronic Fatigue
– problems with Glutamate and NMDA receptors
- Chronic Fatigue Syndrome is associated with hypocortisolemia [low cortisol due to suppression of adrenal glands]] and increased serotonin transmission.
- elevated epinephrine [adrenaline] levels, but not norepinephrine [noradrenaline]
- disruption of ability of nervous system to control immune system
- serotonin levels are elevated, but serotonin activation of hypothalamus-pituitary-adrenal axis is decreased
- adrenal glands decrease in size by 50%
- adrenal atrophy

- Transforming Growth Factor-beta 1 is increased….may cause fatigue by way of decreased motivation for motor behavior

Fibromyalgia
– problems with Glutamate and NMDA receptors

Pre-mentrual Syndrome [PMS] – problems with GABA receptors and progesterone
-Lower protein intake associated with higher ratings of well being.
-Aerobic exercise and strength training are associated with decreased symptoms. Exercise decreases lutenizing hormone, and follicle stimulating hormone. Progesterone levels may decrease with training.
- Progesterone decreases serotonergic activity in the ventromedial hypothalamus.
- Antidepressants have proven effective in relieving symptoms[serotonin antagonists/reuptake inhibitors].
- Worst cases of PMS have decreased serotonin just prior to period.
- Progesterone has long been advocated as the treatment (during luteal phase) for severe premenstrual symptoms. Progesterone increases GABA transmission. GABA transmission may have anti-anxiety effects.
- Progesterone administration restores menstrual flow in ammenorheic athletes.
- Carbohydrates significantly decrease self-reported tension, depression, anger, in less severe cases of PMS.
- During pre-menstrum, higher intake of carbo associated with higher ratings of negative affect, and decreased activity.
- Hot flashes are associated w/androgen deprivation. During cycle, androgens decrease, estrogens increase.
- Prolactin has receptors in several brain areas. PRL may act as a neuromodulator and decrease dopaminergic neurons in non-hypothalamic areas of brain. Non-pituitary PRL may be responsible. PRL may have direct inhibitory effects on dopaminergic neurons.
- Stress turns on prolactin
- elevation of cortisol results in a decrease in progesterone.
- cortisol is able to compete with the action of progesterone.
- Ovarian steriods (Progesterone) may affect GABA-B binding by regulating the density of GABA-B receptors
- Progesterone facilitates GABA activity, thus reducing arousal levels.
????what is estrogen's effect on PRL during menstrual/ovarian cycle???
Behavioral aspects of PMS may be similar to steroid rage, w/similar mechanisms--- blocking of opiods from their receptors by steroids that compete with them for binding sites.
- Opiod modulation of the hypothalamic-pituitary adrenal axis is altered in women with severe PMS possibly due to hyposensitivity of opiate receptors. Sypmtoms result from a "withdrawl" from endogenous opiods. Opiods interfere with cortisol secretion.
- may involve dysregulation of beta endorphin

Bi-polar, **Manic Depression**

-- problems with Glutamate

- people with manic depression have increased number of receptors for mono-amines [dopamine, norepinephrine, serotonin] in the thalamus area
-- loss of hippocampus inter-neurons

Major Depression – problems with Serotonin
- Depression is associated with high cortisol levels and decreased serotonin transmission,
- Drug free depressed patients have;
- lower than normal concentrations of serotonin
- lower than normal tryptophan concentrations
- increased density of binding sites for serotonin
- low numbers of serotonin transporter sites
- Prefrontal Cortex is the place most affected by serotonin dysfunction in depression...in depression serotonin input is abnormal in this area....major area of mood regulation, behavior inhibition
- Psychotic depression -- increased cortisol and dopamine, respond poorly to antidepresants unless neuroleptic is added
- GABA receptors are related to depression
- cortisol downregulates serotonin receptors, which may affect mood and behavior.
- Depression may decrease immunocompetence by influencing opiates impact on natural killer cells and other lymphocytes
Injection of opiods/direct electrical stimulation of the preiaqueductal grey area and scalp electrical stimulation (SES) increase velocity of wound healing. Adaptation to wound stress is enhanced by endogenous opiods. SES increases work capacity by way of increasing endogenous opiods. Enkephalin is believed to cause presynaptic inhibition of incoming pain fibers at their entry into the spinal cord from the periphery. The most important opiate substances are; B-endorphin, met-enkaphalin, leu-enkaphalin, and dynorphin. B-endorphin is in the hypothalumus and pituitary.
- high depression blunts GH response to exercise
- overtraining may decrease GH response to a workout
- brain serotonin levels in patients with major depression is decreased
- decreased activity in prefrontal cortex [dorsal frontal, dorsal lateral]
- decreased size of hippocampus [due to tissue loss]….these decreases could be decreases in

inhibitory cells or decrease in excitory cells

Post Traumatic Stress Disorder
-- Panic Disorder
– problems with Glutamate and NMDA receptors
- brain blood flow levels are decreased
- phyto-estrogens in soy, decrease anxiety

Obsessive Compulsive Disorder – problems with Glutamate and NMDA receptors in caudate nucleus of hypothalamus
- brain blood flow levels are decreased
- elicited by excessive forebrain glutamate output
- 40 – 75% of people with OCD….also have Tourette's syndrome

Pseudo-Seizures – caused by chronic stress, strongly associated with emotional or sexual abuse, especially in children and adolescents.

Schizophrenia
– problems with Glutamate and NMDA receptors
- characterized by increased dopamine content, and increased dopamine receptors
- cognitive therapy is effective in modifying delusions and making changes in psychotic thinking
- schizophrenics may have malfunction of GABA as well as glutamatergic funcitons
- decrease in size and number of excitory neurons in hippocampus
- decrease in size of hippocampus
- decrease in synapses between excitory neurons
- decrease in number of large neurons
- understimulation of receptors
- NMDA receptor malfunction in glutamate neurotransmittion
- hypoglutamatergic problem
- glycine works as an agonist in NMDA receptors
- symptoms = suspiciousness, depression, anger, difficulties concentrating/memory, emergence of odd beliefs, loss of energy, loss of motivation, disturbances in perception…..all can be transient reactions to stressful siturations
- cells in hippocampus and thalamus may be involved affected
- damage to NMDA receptors
- decrease in glutamate receptors
--- AMPA receptors is decreased in hippocampus
--- kainate receptors is decreased in hippocampus
--- NMDA r1 receptors is decreased in conical regions
- dopamine enhancing drugs increase psychosis in schizophrenia.
- Anti-psychotic drugs block dopamine D2 receptors
- sustained activity of neurons in prefrontal cortex causes decreased memory
- volume of gray matter in pre-frontal cortex, decreases
- Beta Amyloid = 39 – 43 amino acids long…..may get into membrane of neurons, and create calcium channels [calcium permeable pores] that allows calcium increase and subsequent necrosis/apoptosis……constituents of membrane lipids may contribute to the pores
- Schizophrenia has been associated with hyperactivity in the ventral hippocampus.
- Schizophrenia patients show reductions in interneurons in the ventral hippocampus
- Replacing interneurons using stem cells can reverse schizophrenia-like deficits.
- aberrant dopamine system function is typically associated with the positive symptoms of the disease
- schizophrenia patients show dysregulated activity in the hippocampus and prefrontal cortex, two regions known to regulate dopamine neuron activity
- deficits in hippocampal and prefrontal cortical function are thought to result, in part, from reductions in inhibitory interneuron function in these brain regions
- symptoms of schizophrenia arise from neural deficits that impair cognitive regulatory control processes
- pattern of neural damage determines the symptom profile
- impact on cognitive regulatory control processes influences whether negative or positive symptoms dominate or exist in relatively equal proportions
- adolescents with early-onset schizophrenia (EOS)
    --- clinical symptoms and cognitive dysfunctions arise from a failure of adequate communication between different brain regions
    --- alterations in the numbers, distribution, ultrastructural integrity of oligodendrocytes of white matter
    --- white matter abnormalities in the anterior cingulum are associated with adolescent EOS

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Multiple Sclerosis
- women - type A personality - visualization/relaxation yields cure
- apoptosis selectively eliminates autoreactive T-cells from the central nervous system
- in MS, T-cell apoptosis is infrequent
- punctuated by exacerbations or relapses in which there is significant clinical worsening, followed by remissions
- remissions caused by a remodeling of the demyelinated axonal membrane via an increase in density of sodium channels
- progression forms of MS are characterized by a downhill course without remissions
- substantial damage to axons as well as myelin in the brain is why patients with progressive MS do not have remissions
- axon degeneration is the cause of "irreversible" neurologic impairment in MS.....MS is more than a demyelinating disease
- T cells are produced that fail to recognize myelin proteins as "self" proteins
- glutamate excitotoxicity destroy schwann cells [glutamate is released by immune cells]
--- decreases in brain cells comes along with de-myelination….and may precede symptoms of de-myelination
--- cells destroyed are excitory neurons [aspartate]
- oral N-acetylglucosamine.....GlcNAc...inhibits growth and function of abnormal T-cells
    - sugar-based supplement corrects defect that induces cells to attack the body in MS
    - proteins on the surface of cells are modified by complex sugar molecules
    - changes in these sugars cause T-cell hyperactivity and autoimmune disease
    - suppress T-cell hyperactivity and autoimmune response by increasing sugar modifications to the T-cell proteins
- neural activity and/or neural pattern might be essential in the maintenance of myelin sheath in adults.
- sigma-1 receptors
    -- located in oligodendrocytes, Schwann cells
    -- affect myelination
- cerebrospinal fluid levels of cobalamin increase
- cobalamin regulates myelino- and oligodendrocyte-trophic epidermal growth factor
- increased cobalamin decreases epidermal growth factor
- decreased EGF may impede CNS remyelination

Dementia
-- defined as a progressive loss of nerve cells that are responsible for normal thought, memory and daily functioning

Vascular Dementia
-- dementia due to neuronal cell death and cerebral atrophy
-- initial pathological changes involve oxidative-induced inflammatory damage to small blood vessels....The resulting ischemia activates amyloid-processing enzymes and other proinflammatory factors that compromise neuronal functions, leading, over time, to the complex lesions that characterize advanced disease
-- other mechanisms.....thrombosis which blocks blood flow or inflammatory changes that destroy the vessel wall and kill the endothelium
-- other mechanisms.....arteriosclerotic damage, is different process from small vessel damage in the cerebral microvessels
-- development of depressive symptoms predicted worse endothelial function
    - endothelial progenitor cells were lower after one year of chronic stress
    - endothelial function may link stress, depression, and cardiovascular disease
-- glucocorticoids interact directly with glucocorticoid receptors on vascular endothelial cells to inhibit tube-like-structure formation.....alterations in cell morphology rather than inhibition of viability, migration or proliferation and may be mediated in part by induction of thrombospodin-1. These findings provide important insights into the anti-angiogenic action of endogenous glucocorticoids in health and disease.
-- hyper-homocysteinemia and β-amyloid induce endothelial dysfunction

Alzheimers
– problems with dopamine, and survival of dopamine producing brain cells,
Something causes oxidant production with insufficient anti-oxidant levels to avoid oxidant damage
With subsequent cell suicide [apoptosis].
- delayed protein turnover results in production of AGE's -- Advanced Glycation End-products
- macrophages internalize and degrade AGE's [similar to how they engorge w/lipid in heart blood vessels]
- Beta amyloid activates the receptor for AGE, called RAGE (R = receptor)
- RAGE is on the surface of neurons and microglia
- activation of RAGE results in generation of reactive oxygen species
- levels of RAGE are 2 - 5 times higher in people with AD
- AGE's are non-enzymatically modified proteins and lipids [ie. Apo E4, LDL]
- glucocorticoids alter antioxidant enzyme capacity
- levels of superoxide dismutase and glutathione peroxidase are decreased in the presence of glucocorticoids
-- in brain, hippocampus affected most
- high GC levels decreases glucose uptake in neurons
- presenilin-2 gene....associated with inherited AD....presenilin-2 functions in an apoptosis pathway downstream of Fas
- mutant presenilin-2 has an even greater ability to induce apoptosis
- beta amyloid plaques alters the apoptotic threshold in neurons.....peptide fragments of beta amyloid can down regulate anti-apoptotic bcl-2, and up regulate apoptotic Bax, making neurons more prone to die, especially in response to oxidative stress
- beta-amyloid increases free radicals when in the presence of free radicals
- anti-oxidants decrease beta-amyloid
- isoforms of APO-E can be anti-oxidants

- beta amyloid decreases/inhibits sodium/potassium pumps in hippocampus neurons
- ApoE4 binds AGE modified plaques…..E4 binds greater than E3
- Nicastrin = protein that upregulates production of beta amyloid precursor protein [APP = amyloid precursor protein]. Production of beta amyloid to toxic levels is due to over production or reduced clearance
- people in early stages of alzheimer's have high cortisol levels, making neurons susceptible to several kinds of insults
- have increased nerve growth factor, decreased brain derived neurotrophic factor…..neurons which fail to get sufficient quantity of neurotrophins, die by apoptosis
- have hyper-perfusion of brain due to decreased vascular function [endothelial cell shapes change] may be due to decreased nitric oxide production of these cells resulting from immune cell adhesion and infiltration [could be same as with heart disease --- production of plaques, atherosclerosis may be a major factor]
- activated microglial cells [can be activated by lipopolysaccharide (LPS)] produce nitric oxide, and TNF-alpha
- cortisol decreases microglial cell production of NO by inhibiting production of nitric oxide synthase
- microglial cells function as brain macrophages
- brain endothelial NO cause vasodialation
- catecholimines inhibit NO production, causes decreased immune function of microglial cells
- glutamate toxicity occurs by NMDA receptor induced calcium entry into cells [AD and ALS may occur by this method]
-- testosterone levels lower
-- testosterone treatment improves cognition
-- testosterone increases nuclear androgen receptors in motor neurons, increase soma size
-- testosterone increases NGF
-- Structures of the medial temporal lobes are recognized to be the primary sites of deterioration in Alzheimer disease
-- Patients with AD demonstrated significant reductions in metabolic activity in the left medial temporal lobe
--- Dementia……estrogen + progestin therapy in postmenopausal women increased dementia and risk of stroke….[JAMA May 28, 2003….page 2651]
--- in AD brains…….presence of anti-brain autoantibodies and immunoglobulins (Ig)
--- brain area = hippocampus, responsible for memory and cognition
--- brain cell destroyer in the hippocampus = accumulation of a protein called beta amyloid or amyloid beta
--- beta amyloid's tool for brain cell death = induces accumulation of a neurotransmitter called glutamate, causing glutamate neuro-toxicity
--- stimulator of beta amyloid plaque accumulation = cortisol, also known as stress hormone, caused by chronic stress
--- immune cells that remove beta amyloid plaques = broadly referred to as microglia, specific cells = macrophages
--- suppressors of macrophage removal of beta amyloid = an item called macrophage inhibitory factor, and chronic stress related cortisol
--- associated with high levels of macrophage inhibitory factor = beta amyloid
- macrophages remove beta amyloid
- macrophage inhibitory factor [MIF] impairs macrophage function
- MIF high in Alzheimer's patients
- stress accelerates progression
- beta-adrenergic receptors activated by stress….amyloid beta peptide production
- beta-amyloid protein enhanced glutamate neurotoxicity
- inflammatory signaling could affect the regulation of glial cell activation
- astrocytes prevent microglial cell cytotoxicity by mechanisms mediated by TGFβ1
- age-related impairment of TGFβ1-Smad3 can reduce protective activation while facilitating cytotoxic activation of microglia, potentiating microglia-mediated neurodegeneration
- Macrophage Inhibitory Factor
-- amyloid beta protein.....essential for the formation of toxic oligomers and Alzheimer plaques....associated macrophage migration inhibitory factor
-- marked increase of MIF levels within the cerebral spinal fluid of Alzheimer patients
beta amyloid
-- decreases glut 4 translocation to brain cell membrane, lowers glucose availability

Parkinson's Disease
– problems with dopamine, and survival of dopamine producing brain cells,
Something causes oxidant production with insufficient anti-oxidant levels to avoid oxidant damage
With subsequent cell suicide [apoptosis].
- marked death of dopaminergic neurons in the substantia nigra
- neurons in the STN become pathologically overactive in Parkinson's disease. These neurons use glutamate.
- Parkinson's is a glutamate hyperactivity syndrome
- dopaminergic neurons are thought to die by apoptosis and necrosis in response to oxidative stress
- marked death of dopaminergic neurons in the substantia nigra
- Sub-Thalmic Nucleus (STN)...reguarded as the most important control structures of the basal ganglia
- have decreased GDNF and bFGF…..neurons which fail to get sufficient quantity of neurotrophins, die by apoptosis
- may be associated with increased homocysteine and decreased folate
--- levodopa treatment increases homocysteine

Amyotrophic lateral sclerosis (ALS)
- mutated SOD-1 gene produces a protein that has toxic effects on motor neurons…..and surrounding cells [ie. glia, etc]
- oxidative neurotoxicity disease, induced by mutation of SOD1 protein
- oxidative neurotoxicity induced mutation (or decreased production/function) of SOD1

- etiology.....early axonal degeneration, smaller diameter fibers
- glutamate toxicity occurs by NMDA receptor induced calcium entry into cells [AD and ALS may occur by this method]
- glutamate toxicity may be responsible for motor neuron degeneration in ALS
- lipid peroxidation and protein glycoxidation are enhanced in the spinal cord motor neurons
- A strong glial reaction typically surrounds the affected upper and lower motor neurons and degenerating descending tracts of ALS patients.
- reactive astrocytes contribute to the excitotoxic damage of motor neurons by decreasing glutamate transport or actively releasing the excitotoxic amino acid.

--- Begins in middle or late life. Motor neuron disease.
- failure in neurotrophic hormone release by muscle
- failure of uptake of the neurotrophic factor by presynaptic axon terminal
- impairment in retrograde axonal transport of the neurotrophic factor to the cell body
- associated with mutations in the gene for superoxide dismutase 1

- motor neurons are lost.....in ventral horn of the spinal cord, brain stem motor neurons, pyramidal neurons in motor cortex
- Ciliary Neurotrophic Factor (CNTF) and neurotrophin 3 levels are decreased in ventral horn of spinal cord
- changes in receptors for IGF-1, BDNF, and CNTF in spinal cord neurons
- NGF levels are decreased in motor cortex
- death ensues once respiratory functions are paralyzed

-- a neurovascular disease
-- impairment of all neurovascular unit components
- blood–brain barrier
- blood–spinal cord barrier

-- Resveratrol protects against the neurotoxicity effects in ALS

Tourette's Syndrome

- elicited by excessive forebrain glutamate output
- 40 – 75% of people with OCD….also have Tourette's syndrome

Austism

-- dysfunction of the intestinal tract, implicated in the development and severity of symptoms
-- association between infection or inflammation during pregnancy and increased risk of autism in the child
-- maternal inflammation during gestation can cause autism-relevant behaviors in the offspring
-- permanent changes in T cell cytokine responses were reported in children with autism

Mental Retardation

- Fragile X mental retardation protein [FMRR1].…….the protein is absent…..most common form of inherited mental retardation
---- synaptogenesis is impaired……dentritic spines may be mis-shapened, immature spine morphology

Obsessive Compulsive Disorder [OCD]

-- patients with OCD have greater trapping of alpha methyl L tryptophan
----- in right hippocampus
----- in left temporal gyrus

-- in OCD, greater temporal lobe activity

Hydrocephalus

-- Normal Pressure Hydrocephalus [NPH]
-- triad.....gait difficulties, urinary incontinence, mental decline
-- chronic and excessive accumulation of cerebro-spinal fluid in the ventricles of the brain.
-- reduction in cerebral blood flow and ventricular dilation
-- dementia-associated NPH....appears as apathy, flat affect and inattention...memory problems are predominant which can lead to the misdiagnosis of Alzheimer's disease
-- stroke which can result in NPH
-- http://www.dorlandhealth.com/adult_and_senior/cip_magazine/The-Overlooked-Brain-Disease_992.html

Traumatic Brain Injury

-- traumatic brain injury activates matrix metalloproteinase 2 and stromal cell derived factor 1α.
-- oxidative stress has significant role in the activation of matrix metalloproteinase 2.
-- matrix metalloproteinase 2 cleaves SDF-1α to generate a neurodegeneration causing fragment.
-- MMP2 cleaved SDF-1α induces caspase-3 and causes apoptotic cell death.

spinal cord injury

-- the region of injury becomes hypoxic due to inadequate blood flow

——- low blood flow is due to neurotransmitters called trace amines
-- trace amines which act on pericytes to constrict blood vessels
——- hyperoxic or inhibition of trace amine improves motor function

Duchenne Muscular Dystrophy (DMD)
- mutation in dystrophin gene
- muscle wasting disease caused by loss of sarcolemmal bound dystrophin
    - results in muscle fiber death
    - utrophin can be upregulated to make up for decreased dystrophin

Vertigo

- problem with vestibular system

Down's Syndrome

- is usually caused by an extra chromosome 21 as a result of meotic non-disjuction
- cells lose telomeres at 2 - 3 times the rate of normal
- decreased removal of ROS (ie. decreased glutathione)

Epilepsy

- postsynaptic increase in density of GABA-(A) receptors as an adaptation to chronic seizures
    - mostly in inhibitory interneurons
    - in hippocampus
- long term potentiation type adaptations may be the etiology of chronic seizures

Attention Deficit Disorder
Attention Deficit Disorder -- deficiency in production and/or usage of serotonin, norepinephrine, dopamine. Traditional treament focusses on restoring neurotransmitter balance by using a psychostimulant (ritalin, amphetamine, etc.).

Curcumin [turmeric]
-- active principle of turmeric used in Indian curry
-- properties....antitumor, antioxidant, antiarthritic, anti-ischemic, anti-inflammatory
-- may inhibit accumulation of beta-amyloid in Alzheimer's
-- rats.....80 mg/kg body weight curcumin for 21 days prevented Parkinson's
-- binds senile plaques
-- promotes disaggregation of existing amyloid deposits
-- prevents aggregation of new amyloid deposits
-- reverses distorted and curvy neurites around senile plaques and repairs neuritic abnormalities
-- longvida curmin crosses blood-brain barrier

brain senescence
-- studies identified the brain's choroid plexus as an interface of continuous dialogue between the brain and blood-borne leukocytes
-- analysis of young and aged mice we found that aging of the choroid plexus is characterized by a unique immunological signature of interferon (IFN-I) response, which we also found in aged human brains
-- we further found that this response is induced by brain-derived signals which are present in the cerebrospinal fluid of aged mice
-- blocking IFN-I signaling within the aged brain partially restored cognitive function and hippocampal neurogenesis and reestablished choroid plexus activity, which was lost in aging
-- our data identify a chronic aging-induced IFN-I response, often associated with antiviral activity, at the brain's choroid plexus, and demonstrate its negative influence on brain function

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Pain

Abnormal, persistent pain may be due to pathological events initiated by NMDA receptors in spinal cord. The adrenal medulla produces a peptide (histogranin), that acts as an NMDA antagonist, thus reducing pain symptoms. Histogranin is an endogenous modulator of NMDA receptor activity.

- antinociceptive ability decreases with oxidant related destruction of spinal opiod receptors “w/aging”. Also due to decrease in dopamine release and motor function
- norepinephrine is involved in brainstem descending inhibitory mechanisms for pain modulation at spinal cord
- opiod containing immune cells migrate to inflammed sites where they release B-endorphin which activates peripheral opiod receptors to inhibit pain.
- Selectins are cell surface glycoproteins that mediate the initial adhesion and rolling, a transient contact leading to a decelaration of leukocytes along the vascular endothelium. This is the first and essential step in the process of leukocyte extravasation into the inflamed sites.
- Selectins mediate the initial phase of immunocyte extravasation into inflamed sites.
- Anti-selectin treatment abolishes peripheral opiod analgesia elicited endogenously (by Stress)
- The immune system uses cell migration not only to fight pathogens but also to control pain injured tissue.
- Pain is exacerbated by measures that inhibit the immigration of opiod-producing cells (ie. NSAIDS)
- in peripheral inflamed tissue, and interaction between immune cell derived opiods and opiod receptors on sensory nerve terminals can result in strong, clinically measurable analgesia.
- Substance P increases postsynaptic depolarization to increase pain signal transmission
  - faciliates glutamate & NMDA receptor activity
- use of magnets.....electromagnetic fields (static magnetic fields) can block action potentials in the dorsal root ganglia
- (1mT/mm) static magnetic field blocks 75% nerve firing in the dorsal root ganglia

--- the “efferent channel” of a pain-control system that “descends” from the brain onto the spinal cord.

- --- rostral ventromedial medulla (RVM),
- --- periaqueductal gray matter (PAG)
- --- nucleus raphe magnus
- --- with their projections to the spinal dorsal horn

-- In models of inflammation, descending inhibition predominates over facilitation in pain circuits with input from the inflamed tissue, and thus attenuates primary hyperalgesia,

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Aging

- premature or excessive cell loss during aging can lead to organ dysfunction and disease.
- The ends of chromosomes, called telomeres, are whittled away until too much is lost for the cell to maintain normal function. At that point, it ceases to replicate. It may be possible to slow down the rate of telomere shortening and therefore slow the aging process.
- In humans the number of oxidative hits to the DNA per cell per day is ~10,000. Oxidative lesions of DNA accumulate with age.
- Free radical induced oxidative damage to mitochondrial DNA or mito.membranes may be an important contributor to senescent ATP production in neuronal terminals. Damage to lysosomal membranes can amplify the destructive process by the release of hydrolytic enzymes.
- Endogenous antioxidant defenses are modulated by the state of physical training. 5 minute interval high intensity training is superior to continuous exercise in upregulating muscle antioxidant defenses.
- Old trained people (62 years old) have a higher Vo2max than young untrained people (25 years old) [51 vs. 46]. Untrained elderly (73yrs.) have higher lipolysis and lower oxidation than young untrained (26yrs.).
- Ederly fail to decrease lipolysis as exercise intensity increases, as one would see in young.
- Cell growth promoters in brain, highest contents in areas of memory and learning such as hippocampus.
  - --- nerve growth factor (NGF)
  - --- brain derived neurotrophic factor (BDNF)
- Chronic exposure to cortisol contributes to neuronal loss (aging of the brain). Chronic stress can cause the production of cortisol which may be the mechanism of impaired learning during stress, and brain degenerative diseases (alzheimers, parkinsons, etc.).
- Damage to synaptic mitochondria cause decreased neurotransmition.
- SOD activity in motorneurons is an important factor in ageing and lifespan determination.

Sexual orientation.....

hypothalamus...

- -- preoptic
- -- uncinate nucleus
- -- suprachiasmatic nucleus
- -- dimorphic nucleus

--- fetal brain develops during the intrauterine period in the male direction through a direct action of testosterone on the developing nerve cells, or in the female direction through the absence of this hormone surge.

--- our gender identity and sexual orientation are programmed or organized into our brain structures when we are still in the womb.

--- sexual differentiation of the genitals takes place in the first two months of pregnancy
--- sexual differentiation of the brain starts in the second half of pregnancy,
--- preoptic hypothalamus has 2 times the cells in a male brain when compared to a female brain.
--- dimorphic nucleus in heterosexual males is much larger than heterosexual females. [in homosexual males...seems to be smaller]
--- uncinate nucleus...male to female transsexuals have a smaller uncinate nucleus compared with heterosexual males.....is smaller in size and neurons.
