Meyer’s: p478-483; p489-490; p498-504

Environmental Agents

Neurotoxicity

* Neurotoxicity—the adverse change in the structure or function of the CNS or PNS
* Neurotoxicant—an element/compound that elicits neurotoxicity by direct/indirect action on one or more components of the adult nervous sytem or the developing nervous system in utero or during childhood
* Can be transient or permanent
* Can manifest long time after exposure
* Mechanisms of neurotoxicity:
  + Oxidative stress
  + Cell death
  + Disruption of signaling pathways
  + Disruptions of homeostatic mechanisms
  + Interference in neurotransmission
  + Interference with synthesis or metabolism of key cellular components and macromolecules
  + Disruption of endocrine system
  + Disruption of morphogenic cells (only in developing nervous system)
  + Interference with morphogenic roles of hormones, NTs and their receptors (only in developing nervous system)
  + Inappropriate stimulation of neuronal differentiation or apoptosis by various mechanisms (only in developing nervous system)
* Risk related to intensity, frequency, and duration of exposure, physical and chemical properties of agent, route of exposure, concentration achieved at the target site, and inherent toxicity of agent itself.
* Young and elderly super vulnerable
  + In young the CNS still developing🡪morphological, function and behavioral changes
  + In elderly, natural aging🡪lack of plasticity and compensatory capacity
* Detecting neurotoxicity:
  + Clinical observations
  + Neuropsychological and behavioral testing
  + Neuroimaging
  + Blood and urine testing

Endocrine Disruptors

* Endocrine disruptors (EDs)—interfere with the endocrine system and may cause adverse effects in development or in the reproductive, nervous, or immune system
* Alters synthesis, metabolism, regulation, or transport of one or more hormones, alters release of hormone from an endocrine gland, or alters normal hormonal response at level of the hormone receptor
* Mothers treated with DES during pregnancy🡪daughters with uncommon vaginal adenocarcinomas
  + DES has estrogen properties
* Genistein (inhibits thyroid hormone metabolism), methoxychlor (insecticide with estrogenic activity), and nonylphenol (chemical in drinking water with estrogenic activity)🡪endocrine disruption.
* Can interfere at any level of endocrine system
  + Can be agonist or antagonist
  + Can bind to receptor and produce nontypical response
  + An interfere with normal hormone synthesis, metabolism, uptake, or release🡪availability of hormones affected
* Effects dose dependent
* Glands of endocrine system: pineal, hypothalamus, pituitary, thyroid, parathyroids, thymus, adrenals, pancreas, ovaries in females, testes in males
  + Secrete hormone into bloodstream
* Neurons synthesize and release polypeptides that act as hormones and affect release of other hormones or hormone actions at target organs
  + Gonadotropin-releasing hormone (GnRH): produced by basal hypothalamus. Stimulates gonadotropin release from anterior pituitary gland.
* Central neuroendocrine system mostly responsible for neural modulation of endocrine function near brain
  + Interaction of nervous and endocrine systems at the level of the hypothalamus, and the posterior and anterior pituitary.
* Diffuse neuroendocrine system: neural-endocrine interactions outside the area of the brain
* Non hormonal NTs (ex. DA, NE, 5-HT) sensitive to endicrine disruption🡪can be influenced by EDs

Hypothalamic—Pituitary—Gonadal (HPG) System

* Hypothalamus interacts with anterior pituitary to control reproductive function
* EDs can alter reproductive function
* EDs can influence developing organism
* Regions of hypothalamus that control reproductive neuroendocrine systems change at specific points in development, which are mediated by exposure to endogenous estrogen and androgen hormones
  + Exogenous hormones perturb normal shit which🡪reproductive neuroendocrine systems fucked up

Hypothalamic—Pituitary—Thyroid (HPT) System

* Hormones released from hypothalamus interact with anterior pituitary
* Thyrotropin-releasing hormone (TRH) released from hypothalamus and interacts in anterior pituitary🡪causes release of thyrotropin (or thyroid—stimulating hormone (TSH))
* TSH stimulates release of thyroid hormones (THs)🡪 accumulation of THs triggers a negative feedback response at level of anterior pituitary to inhibit TRH (are we sure it’s TRH instead of TSH??) release
* Hypothalamus regulates energy and metabolic homeostasis. Changing TH distribution can effect development, metabolism, or adult physiology
* Function of thyroid can be impacted at different points in the TH pathway (fig 17.5)
* TH secreted into blood. Availability to cells can be affected by accessibility of specific carriers or binding proteins in the blood and by cell-specific transporters that control TH uptake into various tissues and cells
* In cell T4 form of TH converted to T3 by deiodinases
  + Many environmental chemicals affect deiodinase activity and🡪symptoms not consistent with hypothyroidism
* TH mimetics could induce hyperthyroidism in some tissues and hypothyroidism in others

Persistent and Semi-Persistent Organic Pollutants

Bisphenol A (BPA)

* Synthetic monomer
* Used in production of plastics
* Primary source of exposure through food and water
* Quickly absorbed from gastrointestinal tract after oral exposure
* Metabolized in liver to BPA-glucoronide
  + Half life less than 6 hours
* We ingest a fuckton of it
* No reports of acute or chronic toxicity in human adults
* Neurotoxicity in children:
  + Trend toward hypotonia (decreased muscle tone) associated with BPA exposure at 16 weeks of gestation
  + BPA levels in mothers associated with externalizing behaviors (hyperactivity and aggression) in children stronger in females than males at 2 years of age
* Endocrine disruption b/c has weak estrogen properties and interaction on nuclear estrogen receptor (ER) and membrane ER
* Crosses placenta easily and binds to alpha-fetoprotein, estrogen-binding protein that normally prevents maternal estrogen from entering fetal circulation.
  + Could increase estrogen bioavailability to fetus
* Binds to thyroid hormone receptor (THR) and antagonizes its activation by T3

Toxic Metals

* Lead, mercury and arsenic
* Among oldest toxicants
* Metals naturally redistributed in environment by geological and biological means—humans magnify distribution.
* Toxicity of metals determined by oxidation state of metal, lipid solubility, cellular dose achieved, duration of exposure, and extent of binding to target biomolecule.
* Mechanisms mediated through mitochondrial damage

Lead (Pb)

* Used in lots of products (paints, gas, ceramics, pipes, solders, batteries)
  + Exposure through food
* GI absorption of ingested water-soluble inorganic lead compouds is 3%-10% in adults and 30-50% in infants and kids
* In blood, most contained in red blood cells, <1% in plasma
* From blood Pb distributed to soft tissues and bones
* Might be preferentially stored in bone of adults
* Doesn’t penetrate BBB of adults but can in kids
* For adults, half-life in blood is 1 month and 20-30 years in skeleton
* Neurotoxicity in adults:
  + Acute high-dose lead poisoning 🡪encephalopathy (brain damage) manifesting as altered mental state, seizures, ataxia and coma
  + Chronic exposures🡪forgetfullness, irritability, weakness, and parasthesia
  + High chronic exposure🡪peripheral neuropathy
* Neurotoxicity in children and the developing nervous system
  + More susceptible to high-dose lead poisoning btu when it happens similar symptoms to adults
  + Chronic blood lead levels of 10 micrograms/dl and higher in kids detrimental to neurodevelopment
    - Impaired cognitive function, behavioral disturbances, attention deficits, hyperactivity, conduct problems, antisocial behavior, delinquency, violence, ADHD
  + Possible reduced gray matter in prefrontal region and effects on myelination (DAMN)
  + Causes decrease in IQ
* Mechanisms of action
  + Effect on calcium metabolism cuz it substitutes itself for calcium and disrupts calcium homeostasis
  + Can🡪apoptosis, excitotoxicity, negatively affected neurotransmitter storage and release, damage to mitochondria, oxidative stress🡪peroxidative damage to lipids and proteins, depletion of antioxidants by binding to sulfhydryls, inactivate antioxidative enzymes, deregulate cell signally, alter cellular membranes, impair synaptic transmission, alter neurotransmitter concentrations, alter neurotransmitter receptor channel properties, and affect protein and gene expression.
  + Fucking up calcium signaling🡪 negative effect on synaptic development and plasticity
  + Lead really just can fuck everything up
  + Inhibits NMDA receptors in hippocampus🡪learning and memory deficits

Mercury (Hg)

* Released from volcanoes and earth’s crust🡪in atmosphere
* In antiseptics, fluorescent light bulbs, laptop monitors, cell phones
  + Improper recycling can release elemental mercury vapor into environment
* Primary source is through consumption of fishies
* Methylmercury passes through placenta and infants can be exposed through mother’s milk
  + Slow/no elimination of methylmercury for infants
* An pass BBB where it’s metabolized to Hg2+
* Concentrates in brain in cerebellum and occipital cortex
* Neurotoxicity in adults
  + Ataxia, impaired gait, increased excitability, tremors, visual field constriction and blindness
  + Inhalation at high concentrations🡪acute interstitial pneumonitis (often fatal)
  + Symptoms might not present for weeks after exposure
  + Causes cerebral atrophy
  + Chronic exposure🡪paresthesia of hands, feet and mouth, impairment of coordination, muscle weakness, mental disturbances, impairment of speech, hearing and peripheral vision.
* Developmental neurotoxicity
  + Fetal Minamata disease—developmental effects observed following in utero exposure to methylmercury in Japan after mass poisoning.
    - Delayed movements, failure to follow visual stimuli, uncoordinated sucking and swallowing
    - Persisting primitive reflexes and markedly impaired coordination
    - Bilateral cerebral atrophy and hypoplasia, abnormal cytoarchitecture, hypoplasia of corpus callosum, defective myelination of white matter, and hydrocephalus
    - Poorly developed and inappropriately located and positioned neurons in CNS
      * Probably result of disrupted neuronal migration and maturation
* Mechanisms of action
  + Chronic exposure to methylmercury🡪accumulation of inorganic and organic mercury in brain
  + Methylmercury hangs around in the brain for a whle (inorganic in brain for years)
  + Disruption in protein synthesis
  + Disrupt signaling pathways involved in cellular communication throughout CNS and PNS
  + Disruption of neuronal migration and neural cytoarchitecture 🡪alteration of neural cell adhesion molecules and disruption of neurocytoskeleton.

Review of endocrine disorders associated with environmental toxicants and possible involved mechanisms. Maqbool et al. (2016)

* Endocrine disrupting chemicals (EDCs)
* From 120 indoor air and dust chemicals 89 organic chemicals are EDC (phthalates etc)

Organ and systemic effects of EDC

Reproductive and developmental effects

* Testicular and ovarian abnormalities
* Reduce number and quality of sperms
* Increase in occurrence of testicular, prostate, and breast cancer
* Possible reproductive malfunctioning in children of pesticides exposed workers
* BPA in plastic
* Aneuploidy in oocytes🡪miscarriages

Carcinogenicity

* Mutagenicity, thyroid gland cancer, prostate cencer, metabolic diseases, cardiovascular problems
* Toxicity often develops during developmental stages of diff organs
* Tobacco smoke🡪lung and alveolar cancer
* Carbamates 🡪leukemia in offspring
* Pesticides 🡪cancers and shit

Effect on thyroid system