07 - 33_Neurochemistry

01 - 1. Synaptic transmission

1. Synaptic transmission

1. Synaptic transmission The presynaptic neuron synthesises, transports and stores the chemical messenger (neurotransmitter). Synthesis takes place in cell body / soma which contains the essential protein synthesis machinery. From here axonal transport occurs, and the neurotransmitter reaches the synaptic terminal. Before its eventual release, the neurotransmitter is stored within the synaptic vesicle. The release takes place through the process of membrane fusion and exocytosis. Upon release, the neurotransmitter occupies receptors present on the surface of the postsynaptic neuronal membrane. Some of the neurotransmitter molecules will also act on autoreceptors that are present in the presynaptic neuronal membrane. Such autoreceptor activity is considered to be crucuial for feedback inhibition of the neurotransmitter synthesis and release. Neurotransmitters exhibit specificity in receptor interaction. One neurotransmitter can have more than one receptor types, but within a given receptor site only a particular chemical conformation can be accommodated (lock and key). Receptors have a finite number and thus get saturated if there is an over secretion of neurotransmitter. Receptor binding is often competitive; relative synaptic concentrations of competing molecules decide the eventual degree of receptor activity. Most receptors are bound reversibly i.e. following dissociation of the neurotransmitter; the receptor falls back to its physiological status quo. Some molecules can act irreversibly producing structural alterations in the protein of receptor complexes. After synaptic release and activity, cessation of neurotransmitter action takes place via
2. Reuptake back to presynaptic neuron via special transporters (e.g. monoamine transporters)
3. Enzymatic breakdown at the cleft (e.g. via COMT/MAO-A enzyme)
4. Removed by glia or plasma circulation (e.g. glutamate shuttle)

 Feedback control of a neurotransmitter may exist at various points

1. Control of presynaptic synthesis
2. Regulation of release
3. Reuptake regulation
4. Autoreceptor mediated presynaptic inhibition
5. Independent postsynaptic inhibition via a different neuronal network Neurotransmitters

Monoamines Amino acids Peptides Dopamine Norepinephrine Epinephrine Serotonin Acetylcholine Histamine GABA Glycine Glutamate

Endorphins Cholecystokinin Neurotensin Neuropeptide Y Leptin Ghrelin

02 - 2. Classification of receptors

2. Classification of receptors

© SPMM Course 2. Classification of receptors Receptors may be categorized into three categories:

(1) Ligand-gated channels (ionotropic), in which binding of a chemical messenger alters the

probability of opening of transmembrane pores or channels;

(2) Those in which the receptor proteins are coupled to intracellular G proteins as transducing

elements (metabotropic);

(3) Those termed ligand-dependent regulators of nuclear transcription (nuclear receptors). Ionotropic or ion channel receptors result in fast response (GABAA benzodiazepine); G protein coupling (metabotropic) is comparatively a slower process (most antipsychotics, antidepressants). Ion channel receptors are made up of four or five protein subunits making up a pore like structure. The GABA-A receptor's structure is typical of most ligand-gated (ionotropic) receptors [‘doughnut with a hole in the centre’ or ‘rosette’ shaped]. Each protein subunit is a string of amino acids which passes in and out of the cell membrane four times. At the extracellular end of this string is a large N-terminal; this end-chain is thought to mediate GABA-channel interactions. In the middle of the string is a large intracellular loop of amino acids with four sites where phosphorylation occurs. Inhibitory neurotransmitter action leads to the entry of Cl- while excitatory action results in the entry of Ca2+ or other cations. Ionotropic receptors include GABAA, NMDA, the 5HT3 subtype of serotonin receptors. G-protein-coupled metabotropic receptors are proteins that span the cell membrane seven times (serpentine receptors). G protein-coupled receptors act via cyclase mediated second messenger activation (GTP, ATP, etc.). Gs-proteins are stimulatory; Gi-proteins inhibit the adenylate cyclase. A third variant of G-protein receptors acts via phospholipase C. Metabotropic receptors influence protein synthesis eventually thus producing longer lasting effects. Metabotropic receptors include DA receptors, most 5HT receptors except 5HT-3, NEN and neuropeptides including opioid receptors are G coupled. Nuclear receptors such as glucocorticoid receptors are part of a superfamily of receptors that have a cysteine-rich DNA-binding domain, a ligand-binding domain, and a variable amino terminal region. Upon appropriate ligand binding, a nuclear receptor becomes a transcription factor and binds in turn to DNA via zinc fingers. Other nuclear receptors include the receptors for progesterone, androgen, and 1,25dihydroxycholecalciferol (Vitamin D). Many receptors of this family are orphan receptors, for

which the ligands are still unidentified. The glucocorticoid receptor is located mainly in the cytoplasm but migrates to the nucleus as soon as it binds its ligand. In contrast, the estrogen and the triiodothyronine (T3) receptors are retained in the nucleus and bind hormones directly in the nucleus itself.

03 - 3. Dopamine

3. Dopamine

•tyrosine l-dopa dopamine Source Source •tyrosine hydroxylase Rate limiting step Rate limiting step •Monoamine oxidase (MAO) & Catechol-o-methyl transferase (COMT). •MAO-A more selectively metabolizes norepinephrine and serotonin •MAO-B more selectively metabolizes dopamine. Breakdown enzymes Breakdown enzymes •Homovanillic acid Breakdown product Breakdown product •Dopamine transporter (cocaine inhibits this transported) Reuptake Reuptake •Motivation, novelty seeking, reward circuitry (addictions), arousal and motor movement gating in basal ganglia Function Function •5 types; D1 to D5 . All are G protein coupled •D1-like D1 & D 5; increase adenylate cyclase (stimulatory). D1 exclusively postsynaptic; resistant to antagonism. D5 more limbic in distribution; 10 times higher dopamine affinity •D2-like D2,3 & 4 ; decrease adenylate cyclase (inhibitory). D4 is found primarily in the frontal cortex and clozapine has a high affinity. D4-selective antagonists do not have antipsychotic efficacy. Receptors Receptors •Levels low in Parkinson’s; high in psychosis especially at mesolimbic area; may be low in anhedonia and negative symptoms in mesocortical area. Disorders Disorders

04 - 4. Noradrenaline

4. Noradrenaline

•tyrosine l-dopa dopamine norepinephrine epinephrine Source Source •tyrosine hydroxylase Rate limiting step Rate limiting step •dopamine-b-hydroxylase modulates norepinephrine production; phenylethanolamine-N-methyltransferase modulates conversion of NEN to epinephrine. Synthetic enzymes Synthetic enzymes •Monoamine oxidase (MAO – A especially) & Catechol-o-methyl transferase (COMT). Breakdown enzymes Breakdown enzymes •3-methoxy-4-hydroxyphenylglycol (MHPG) & VMA – vanillyl mandelic acid. •MHPG is the major metabolite in CNS while VMA is major metabolite from peripheral nervous system/endocrine system. Breakdown product Breakdown product •noradrenaline reuptake channel (tricyclics, reboxetine inhibit this) Reuptake Reuptake •arousal, anxiety, mood regulation, autonomic mediation Function Function •2 major types; α and β. •α divided into a1 and a2 •α1 receptors phospholipase C coupled; mostly postsynaptic •α2 receptors Gi coupled ; mostly presynaptic autoreceptors •β-receptors Gs coupled; predominate locus ceruleus – may regulate a •β1-receptors – high affinity to norepinephrine and β2-receptors – high affinity to epinephrine. Receptors Receptors •Levels low in depression and abnormal in panic/anxiety disorders. Disorders Disorders

05 - 5. Serotonin

5. Serotonin

•tryptophan 5 hydroxy l-tryptophan serotonin Source Source •availability of tryptophan (hence it is possible to conduct tryptophan depletion studies and manipulate 5HT system) Rate limiting step Rate limiting step •tryptophan hydroxylase Synthetic enzymes Synthetic enzymes •MAO (preferentially MAO-A) Breakdown enzymes Breakdown enzymes •5-hydroxyindoleacetic acid (5-HIAA) Breakdown product Breakdown product •Serotonin reuptake channel (tricyclics, SSRIs inhibit this) Reuptake Reuptake •mood, perception of pain, feeding, sleep-wake cycle, motor activity, sexual behaviour, and temperature regulation. Function Function •14 known subtypes of serotonin receptors (5-HT1A, 5-HT1B, 5-HT1D, 5-HT1E, 5-HT1F, 5HT2A, 5-HT2B, 5-HT2C, 5-HT3, 5-HT4, 5-HT5A, 5-HT5B, 5-HT6, and 5-HT7) •All except 5-HT3 are G-protein-coupled receptors; 5HT3 predominant in gut; associated with motility. •5-HT1A receptors – Gi coupled postsynaptic; antidepressant response; sexual behaviour •5-HT1B receptors – Gi coupled presynaptic; •5-HT1D receptors – Gi coupled - both presynaptic and postsynaptic. •5-HT2 receptors - phospholipase C coupled; postsynaptic; antagonism leads to antipsychotic response (atypicals) and sedation; LSD causes 5-HT2 stimulation; down regulation noted after antidepressant treatment / ECT. •5-HT6 may be involved in antidepressant action •5-HT7 - regulation of circadian rhythm Receptors Receptors •low serotonin levels increased depression, aggression, suicide, and impulsivity; regulate dopamine system – role in psychosis Disorders Disorders

 Receptor Action 5HT1A Antidepressant (agonist), anxiolytics (partial agonist) 5HT1B Aggression 5HT1D Antimigraine (antagonist) 5HT2A Antipsychotic (antagonist); hallucinogens (agonist / partial agonist); implicated in working memory; also seen in platelets and smooth muscles 5HT2B Stimulation may produce cardiac valvular fibrosis (dexfenfluramine) 5HT2C Anxiogenic and anorexic effect (agonists) 5HT3 Antiemetic (antagonist) 5HT6 Possible antipsychotic/antidepressant action (antagonism) 5HT7 Regulation of circadian rhythm

DOPA decarboxylase (DDC) “is an enzyme implicated in 2 metabolic pathways, synthesizing two important neurotransmitters, dopamine and serotonin (Christenson et al., 1972). Following the hydroxylation of tyrosine to form L-dihydroxyphenylalanine (L-DOPA), catalyzed by tyrosine hydroxylase, DDC decarboxylates L-DOPA to form dopamine. This neurotransmitter is found in different areas of the brain and is particularly abundant in basal ganglia. Dopamine is also produced by DDC in the sympathetic nervous system and is the precursor of the catecholaminergic hormones, noradrenaline and adrenaline in the adrenal medulla”. In the nervous system, tryptophan hydroxylase produces 5-OH tryptophan, which is decarboxylated by DDC, giving rise to serotonin. DDC is a homodimeric, pyridoxal phosphate-dependent enzyme. (Excerpt from

www.omim.org)

06 - 6. Acetylcholine

6. Acetylcholine

•choline and acetyl-coenzyme A Source Source •availability of choline Rate limiting step Rate limiting step •choline acetyltransferase Synthetic enzymes Synthetic enzymes •acetylcholinesterase – rapid metabolism Breakdown enzymes Breakdown enzymes •Choline Breakdown product Breakdown product •no reuptake. Degraded choline is re up-taken and recycled. Reuptake Reuptake •Modulate arousal, learning, memory, rapid eye movement sleep, pain perception, and thirst and parasympathetic mediation. Function Function •Muscarinic receptors - G-protein-coupled. •Five subtypes (M1, M2, M3, M4, and M5) •Nicotinic receptors - ion channels; •more in peripheral parasympathetic system; •Less common than M receptors in CNS – mediates attention. Receptors Receptors •reduced cholinergic function in Alzheimer's dementia; dopamine balance affected in Parkinson’s Disorders Disorders

07 - 7. GABA

7. GABA

•Glutamic acid (glutamate) Source Source •glutamic acid decarboxylase (GAD) catalysis Rate limiting step Rate limiting step •glutamic acid decarboxylase (GAD) Synthetic enzymes Synthetic enzymes •GABA transaminase Breakdown enzymes Breakdown enzymes •Broken down to glutamate, and then eventually to succinic acid Breakdown product Breakdown product •reuptake into both presynaptic nerve terminals and surrounding glial cells; uptake system is bidirectional and both temperature- and ion-dependent process; (inhibited by tiagabine) Reuptake Reuptake •Mediates anxiety, seizure cessation, and actions of benzodiazepines, barbiturates, and alcohol. Function Function •GABAA and GABAB •GABAA – opens chloride channel; inhibitory – leads to hyperpolarization; made of five subunits and at least 14 subunit subtypes •GABAB receptor is G-protein-coupled; baclofen is selective agonist Receptors Receptors •Role in anxiety disorders and alcoholism; may have a role in many other disorders including epilepsy and Huntington’s. Disorders Disorders

08 - 8. Glutamate

8. Glutamate

•1. from 2-oxoglutarate and aspartate by aspartate aminotransferase, •2. from glutamine by glutaminase, or •3. from 2-oxoglutarate by ornithine aminotransferase Source Source •accumulation of precursors such as glutamine or by end-product inhibition Regulation Regulation •glutaminase Synthetic enzymes Synthetic enzymes •Glutamate dehydrogenase, glutamine synthetase Breakdown enzymes Breakdown enzymes •Broken down to glutamine or alpha-ketoglutarate Breakdown product Breakdown product •Largely glial uptake with conversion to glutamine Reuptake Reuptake •Important metabolic role – intermediary in oxidation pathway (malate shuttle), immediate precursor of all GABA in CNS, intermediary in ammonia cycle; NMDA - memory acquisition, developmental plasticity, epilepsy, and ischemic brain injury. NMDA receptor mediates long-term potentiation Function Function •metabotropic - 8 in total; 3 groups. Group I - mGluR1& mGluR5 – linked to phospholipase C •Ionotropic: NMDA and non-NMDA •NMDA - made up of subunits with distinct binding sites for glutamate, glycine, phencyclidine (PCP), magnesium, and zinc. •Non NMDA – kainate binding or AMPA type. Receptors Receptors •excitotoxic glutamate toxicity in stroke/schizophrenia/seizures suspected. NMDA antagonists can cause hallucinations – e.g. PCP, ketamine Disorders Disorders

09 - 9. Glycine

9. Glycine

10 - 10. Endocannabinoids

10. Endocannabinoids

11 - 11. Neurotrophins

11. Neurotrophins

© SPMM Course 9. Glycine Glycine is the primary inhibitory neurotransmitter in the spinal cord It has the simplest structure of all aminoacids It is synthesized primarily from serine by serine trans-hydroxymethylase and glycerate dehydrogenase, both of which are rate-limiting steps. Glycine acts as a ‘mandatory adjunctive neurotransmitter’ for glutamate receptors; the excitatory glycine site on the NMDA receptor is called non-strychnine-sensitive glycine receptor. Strychnine-sensitive glycine receptor is an inhibitory receptor seen in the spinal cord where glycine acts independently. Facilitating glycine transmission can help reduce negative symptoms of schizophrenia. An experimental agent called bitopertin is a glycine reuptake inhibitor that has shown some early promise in reducing negative symptoms.

10. Endocannabinoids Two endogenous cannabinoid substances

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Anandamide (a weak ligand) and 2arachnidonylglycerol (a strong ligand) are formed from arachidonic acid and ethanolamine. The two types of cannabinoid receptors, central (CB1) and peripheral (CB2), both bind tetrahydrocannabinol (THC), the active ingredient of marijuana. Anandamide lowers intraocular pressure, decreases activity level, and relieves pain.

11. Neurotrophins These are substances that act as polypeptide growth factors influencing proliferation and differentiation of neurons and glial cells. The best-characterised factors are Nerve growth factor (NGF); brain derived neurotrophic factor (BDNF), neurotrophin 3 and neurotrophin 4. According to neurotrophin hypothesis neurons compete during development for the limited resource of growth factors in the target region. Those neurons that are highly responsive, e.g. via high affinity binding sites, survive while others undergo programmed cell death. Incorrect targeting of axons may also lead to apoptosis (programmed cell death). BDNF may have a role in long-term potentiation (LTP) of memory. In animals, chronic stress leads to down regulation of BDNF. BDNF has been shown to have trophic effects on serotonergic and noradrenergic neurons. SSRIs and other antidepressants including ECT up regulate BDNF. The time course of this up regulation coincides with observed therapeutic actions of antidepressant interventions. A single nucleotide polymorphism in the BDNF gene on chromosome 11p13 results in an amino-acid substitution of valine (val) with methionine (met) at codon 66 (Val66Met) reducing BDNF activity. BDNF met/met mice demonstrate increased anxiety. Clinical studies in humans have demonstrated that subjects with the Val66Met allele have impaired hippocampal activation and performance. It is controversial if BDNF polymorphism increases the risk of clinical disorders or not.

12 - 12. Some clinical implications

12. Some clinical implications

β ADRENOCEPTOR Chronic antidepressant treatment induces a reduction in β adrenoreceptor density around 2 weeks after starting antidepressants; this correlates with therapeutic effects.

Unmedicated suicide victims show higher density of β adrenoreceptors. β blockade can reduce peripheral features of anxiety driven by sympathetic overdrive. 5HT & DEPRESSION An increased density of 5HT2 binding sites has been shown in post mortem studies of depressed / suicidal patients. The increase in 5HT2A receptors is most prominent in dorsolateral prefrontal cortex and in platelets of medication naïve patients. A reduction in 5HT1A receptors has also been noted in cortex

Long-term antidepressant treatment has been shown to reduce 5HT2 receptors and increase 5HT1A function. But these changes may not be causative of antidepressant action as they predate any clinical response to antidepressant therapy

Most directly acting 5HT1A agonists have poor antidepressant activity.

Ach & LEWY BODY DEMENTIA Brain acetylcholine levels are reduced in DLB similar to Alzheimer’s. Cortical choline acetyl transferase (ChAT) is reduced to a greater extent (85%) in patients with hallucinations in Lewy body dementia than in those without hallucinations (50%). This may partially explain the altered sleep-wake patterns seen in DLB and also the response of hallucinations to acetylcholinesterase inhibitors ABERRANT SALIENCE Kapur proposed that in the normal individual, the role of mesolimbic dopamine is to attach significance or ‘salience’ to an external stimulus, or an internal thought. This converts a neutral piece of information into an attention grabbing one (Kapur, 2003).

In acute psychosis where hyperdopaminergic state is noted in mesolimbic system, insignificant events and perceptions receive inappropriate salience leading to delusional elaborations.

Antipsychotics are claimed to "dampen the salience" of these abnormal experiences - do not erase the symptoms - but provide the platform for a process of psychological resolution.

  http://omim.org/entry/107930   Kapur, S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. Am J Psychiatry 2003; 160   Angelucci et al. BDNF in schizophrenia, depression and corresponding animal models. Molecular Psychiatry (2005) 10, 345–352   Artigas F. Serotonin receptors involved in antidepressant effects. Pharmacology & Therapeutics, 2013; 119-31