Schizophrenia

The nature and the common symptoms

Schizophrenia affects about 1% of the population. Because it affects young people so is often chronic and is usually highly disabling. The symptoms can be classified into two aspects. The **negative symptoms contain blunted (flat) effects**, **hallucinations, alogia, avolition** and anhedonia. The **positive symptoms include delusions, disorganised behaviour**, and lack of insight. Schizophrenia can present dramatically usually in young people, with predominantly positive features or more insidiously in older patients with negative features. A characteristic feature of schizophrenia is a defect in selective attention. The ability of schizophrenia patients to discriminate between significant and insignificant stimuli seems to be impaired.

Aetiology and pathogenesis of schizophrenia.

The causes of schizophrenia consist of a combination of genetic and environmental factors. In a pair of identical twins, one of whom has schizophrenia, the probability of the other being affected is only about 50%, pointing towards the importance of environmental factors. The most robust associations are with genes that control neuronal development, **these include C4A**, which will process synapse **elimination when overexpressed**. The **malfunction of NMDA receptors** is further implicated by **D-amino acid oxidase,** the enzyme responsible for **metabolising D-serine**, an allosteric modulator of NMDA receptors. Among other suggested genes, some are involved in monoamine transmission in the central nervous system.

The main neurotransmitters thought to be involved in the pathogenesis of schizophrenia are dopamine and glutamate. One of the pharmacological evidence of dopamine theory is **Amphetamine** which releases dopamine and can produce in humans a behavioural syndrome reminiscent of an acute schizophrenia episode. Also, hallucinations are a side effect of levodopa and dopamine agonists used for PD. Furthermore, brain imaging studies have revealed an **increased dopamine synthesis and release in the striatum of schizophrenic patients.** Therapeutically inhibiting dopaminergic transmission in the limbic system might be desirable yet enhance dopaminergic transmission in the prefrontal cortex.

Different symptoms of schizophrenia appear to result from malfunctions in different neuronal circuits. Changes in the **mesolimbic pathway** (the neuronal projection from the ventral tegmental area (VTA) to the nucleus accumbens, amygdala and hippocampus) are associated with positive symptoms. In contrast, negative symptoms are related to changes in the prefrontal cortex which receives input from the VTA via the mesocortical pathway and which projects to the nucleus accumbens and dorsal striatum.

In the brains of schizophrenic patients, expression of the glutamate **uptake transporter VGLUT1** is reduced, which may indicate a disruption of glutamatergic nerve terminals, evident as a reduction in the function of NMAD receptors. NMDA receptor hypofunction is thought to reduce the level of activity in **mesocortical dopaminergic neurons.** This would result in a decrease in dopamine release in the prefrontal cortex and could thus give rise **to negative symptoms of schizophrenia**. This shows stereotypic behaviours and reduced social interaction that are features of human schizophrenia and that respond to antipsychotic drugs. In addition, NMDA receptor hypofunction on **GABAergic neurons would reduce inhibition** of the excitatory cortical input to the VTA and thus enhance activity in the **mesolimbic dopaminergic pathway.** Thus NMDA receptor hypofunction could give rise to enhanced dopamine release in limbic areas such as the nucleus accumbens, producing **positive symptoms.**

CLASSIFICATION OF ANTIPSYCHOTIC DRUGS

The antipsychotic drugs can be divided into two groups – those drugs that were originally developed (e.g. **chlorpromazine, haloperidol** and many similar compounds), often referred to as first-generation. The primary mechanism of first-generation drugs **is D2 dopamine receptor blockade**. Typical or conventional antipsychotic drugs, and more recently developed agents (e.g. **clozapine, risperidone**), which are termed second-generation or atypical antipsychotic drugs. They are **blockade of 5-HT2A receptors.** 5-HT2A receptors play a crucial role in regulating the dopamine system. Antagonism of these receptors in the prefrontal cortex reduces serotonin's inhibitory effect on dopamine neurons, thereby increasing dopamine release through the mesolimbic pathway. Second-generation thought to help reduce negative symptoms and cognitive deficits of schizophrenia while reducing the motor side effects associated with dopamine antagonism. This dual-action mechanism provides a balanced therapeutic effect and lowers the risk of extrapyramidal symptoms. Also, the **NMDA agonists (eg. D-serine, glycine, sarcosine)** improve symptoms and have therapeutic benefits as well.