Brain disorders involving the serotonergic system.

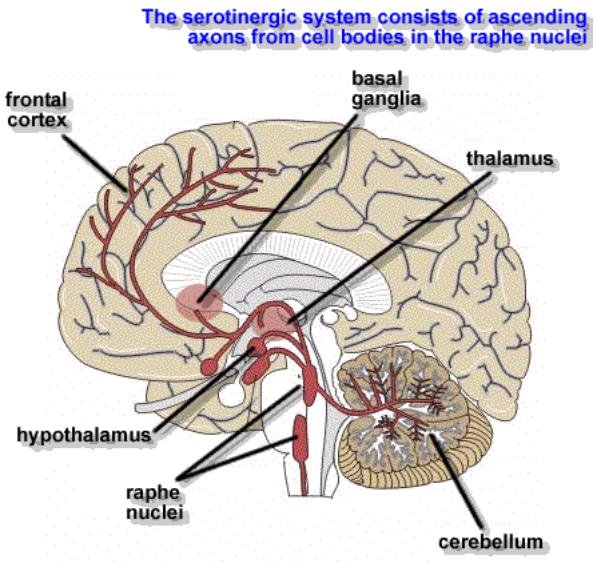
Serotonin (5-HT, 5-hydroxytriptophan) is a monoamine neurotransmitter from the group of biogenic amines. Serotonergic neurons are involved in broad range of physiological and behavioural processes such as cardiovascular regulation, respiration, thermoregulation, mood, circadian cycles, appetite, pain sensitivity, sexual behaviour, cognition, learning etc. They play important part in a range of psychiatric disorders (anxiety disorders, depression, schizophrenia) as well as less structured behavioural impulse-related disorders (violence, substance abuse, obsessive control, gambling addiction, attention deficit disorder etc.).

Structure and components of serotonergic system.

There is only small number of serotonergic neurons in the brain and they are scattered in hindbrain and midbrain. Largely they are present in the brainstem raphe nuclei and some particular regions of reticular formation (9 nuclei all together). Two raphe nuclei, median and dorsal, project to the higher brain structures. Serotonin is mostly produced in raphe nuclei.

There are only around 300,000 serotonergic neurons in human brain, but they have an extensive axonal projection system which has huge number of collateral branches. As a result, serotonergic system reaches almost all areas of central nervous system.

Fig. 1. Structure of serotonergic system



Serotonergic system is one of the evolutionary oldest and seems to be involved in various inhibitory responses throughout the central nervous system. It opposes most of other amine systems in terms of behavioural and sensory output.

The outcome of the serotonin release in the synapse depends on the type of receptor it binds to on the target cell. At least 17 types of receptors responding to serotonin were discovered.

The firing and release of serotonin is controlled by two major receptors: 5-HT 1A and 5-HT 1B. Both receptors are auto receptors – their stimulation results in the decrease of serotonin release. The 5-HT 1A receptors are found on the bodies and dendrites of serotonergic cells as well as on the postsynaptic targets. Stimulation of 5-HT 1A receptors leads to the inhibition of serotonin synthesis and neuronal firing by serotonergic cells. The 5-HT 1B receptors are located mostly at the sites of serotonin release and their activation leads to the inhibition of serotonin release.

Auto receptor 5-HT 1D and receptor 5-HT 3 are also inhibitory. Receptors 5-HT 1C and 5-HT 2 produce postsynaptic excitation.

The 5-HT 3 receptors are ion channel. All other receptors structurally belong to the class of G-protein coupled receptors.

Lots of proteins and enzymes are involved in the metabolism and reutilization of serotonin and can influence its level. Mutations and defects in corresponding genes affect the levels of serotonin or sensitivity to serotonin and may cause behavioural changes.

The plasma membrane Serotonin Transporter (SERT) is responsible for reuptake of released serotonin from the synaptic gaps and found on the terminals of axons as well as cell bodies and dendrites. This protein is targeted by a number of psychoactive drugs (psychostimulants and antidepressants) that slow down the transport activity and thus inhibit the reuptake of the neurotransmitter.

Tryptophan Hydroxylase (ThP) is one of the enzymes involved in biosynthesis of serotonin. The step catalysed by this enzyme is rate limiting and as a result ThP controls the overall rate of serotonin synthesis. The enzyme itself can be controlled via phosphorylation and inhibition by the end product. Another protein, vesicular monoamine transporter (VMAT), is involved in the transport of monoamines like serotonin into the synaptic vesicles.

The mitochondrial enzyme MAO-A (monoaminooxidase A) metabolizes serotonin by deaminating it. Inhibition of this enzyme leads to accumulation of serotonin and has positive effect in releasing the symptoms caused by lowered concentration of serotonin.

Changes in behaviour caused by changes in serotonergic activity.

Alterations of the genes encoding the above mentioned proteins and receptors result in the changes of the levels of serotonin and cause various behavioural changes.

Defects of 5-HT 1A receptors lead to the increase in anxiety (Gingrich and Han, 2001). The decrease of the level of serotonin and its metabolite 5-HTII, 5-hydroxyindoleacetic acid generated by the action of monoaminooxidase A, was associated with violent behaviour and antisocial personality disorder (Linnoila et al., 1994). Increased level of serotonin in early life, associated with decreased activity of monoaminooxidase A, seems to be correlating with the higher risk of violent behaviour and aggression in the adulthood (Pine et al., 1997).

Abnormalities in serotonin signalling are important in development of schizophrenia (serotonin hypothesis of schizophrenia). Antagonists of 5-HT 2A receptors in conjunction with antagonists of dopamine receptors are effective for schizophrenia (Alex and Perek, 2007).

Various agonists and antagonists of serotonin receptors induce a variety of behavioural responses. Many drugs are acting via serotonergic system. For instance, the 5-HT 2A receptors seem to be involved in the mechanism of LSD, one of the strongest hallucinogens known. LSD binding with this receptor is an initial event leading to general decrease in inhibitory action of serotonergic system. Certain similarities between the effects of LSD and mystical experience makes some authors to speculate that serotonergic system is also involved in our perception of religious experience (Goodman, 2002).

Connections between serotonergic activity and suicidal behaviour.

Researchers argue that the suicidal behaviour can be connected to other characteristics such as impulsiveness and aggression and some individuals are more vulnerable due to underlying genetic factors. Some authors estimate that genetic factors play role in 30 – 50% of suicides (Brent and Mann, 2005).

Low serotonergic activity is associated with depressions and suicidal behaviour. There are a number of genetic factors leading to decreased level of serotonergic activity in certain areas of the brain. They contribute to the development of various psychopathologies.

Correlation between suicide attempts and decreased level of 5-HAII (which is assumed to indicate the decreased level of serotonin as well) in cerebrospinal fluid was reported for patients with major depressions.

Several genetic alterations in the gene for tryptophan hydroxylase (TpH) were reported to be associated with suicidal behaviour (Arango et al., 2003 and references herein). As mentioned earlier, TpH enzyme catalyses the rate limiting step of serotonin biosynthesis, and therefore its genetic alterations can easily affect the level of this mediator. There are two isoforms of TPH gene, TPH1 and TPH2. The second one is more likely to be associated with suicides since it is expressed in the brain. The higher level of TPH2 mRNA was observed in depressed patients who attempted suicides comparing with depressed patients who didn't. A variety of polymorphisms in THP2 was analysed but the data are still inconsistent (Mann et al., 2008).

The density of serotonin transporter 5-HTT binding sites on serotonergic neurons and nerve terminals is decreased in orbital cortex of suicide victims and is widespread in depression (Mann et al., 2000). Commonly observed polymorphism 5-HTTLPR has 44 base pairs deletion in the 5'-regulatory element which results in a shorter form of promoter region and differential (decreased) expression of the transporter gene. Decreased level of transporter results in decreased reuptake of serotonin. Correlation between 5-HTTLPR and suicidal behaviour is well studied but the straightforward interpretation of results is not always possible (Ozalp, 2009).

Impulsive aggressive and sexual behaviour was well documented in mice lacking 5-HA 1B receptor gene homologous to the human version. One common polymorphism in human 5-HT 1B receptor (G861C) seems to be associated with a history of suicide attempts, probably due to smaller number of 5-HT 1B binding sites. The results of these studies are not conclusive though (Ozalp, 2009, Arango et al., 2003 and references herein).

Several studies report the connection between suicidal behaviour and the elevated level of 5-HT 2A receptor binding in prefrontal cortex. These receptors are mostly located on serotonin-receptive postsynaptic neurons of cerebral cortex. Elevated level of these receptors is usually interpreted as a result of up-regulation in response

to lowered level of serotonin. But as in the case of 5-HT 1B receptor, there is a disagreement in the literature regarding how significant is correlation between the alterations in 5-HT 2B and suicide attempts (Arango et al., 2003 and references herein; Ozalp, 2009 and references herein).

There is no single "suicide gene" in human genome, but some genetic mutations and alterations in the genes involved in regulation of serotonergic system certainly create conditions for higher likelihood of deep depressions and suicides (Arango et al., 2003). Suicidal behaviour, like most of other psychopathological disorders, involves complex gene interaction and can't be explained by only one single factor. The polymorphism studies provide clear evidences that suicidal tendencies can be inherited by children from parents, and individuals that are genetically prone would have higher probability of committing suicide if they are faced with adverse life events or suffer from psychopathologies.

Conclusion

Serotonergic system doesn't seem to have a direct control of anything critical but it participates in the vast variety of behavioural responses and modulates them. As a result, its involvements can be seen in a significant number of diseases and conditions with complex etiology such as schizophrenia and depression. The complexity of serotonergic system presents a challenge for developing the drugs targeting its components: in addition to desirable effects various side effects associated with the same targets are usually observed.

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