Functions

Dopamine is a catecholamine that is mainly used as a neurotransmitter in the CNS but does also have some functions in the periphery. In the kidney, dopamine is considered having a promoting effect on natriuresis, it stimulates the exocrine secretion and vasodilatation in the pancreas and increases the blood-flow in the renal mesenteric, coronary and cerebral vessels. (Thorner, 1975)

Despite the effects of dopamine in the periphery in the body of a human, this review is mainly focusing on its relevance as a neurotransmitter in the central nervous system.

Dopaminergic fibers are the most present in four pathways, one of which is the nigro-striatal pathway, were dopaminergic neurons from the substantia nigra in the midbrain connect GABAergic basal ganglions in the dorsal striatum. The degeneration of this pathway leads to Parkinson’s disease and to typical symptoms of motor skills deficiency This reflects the natural functions of this pathway, the control of motor function and learning of new motor skills and his overall role in movement. (Ayano, 2016; Aminoff, 2004)

Dopamine released in the tuberoinfundibular pathway is the main inhibitor of the prolactin secretion in the anterior pituitary gland. Dopamine is produced in the arcuate nucleus of the hypothalamus and is transported to the median eminence, where it gets released into the blood vessels, which supply the pituitary gland. Dopamine then acts on lactotrophic cells that produce prolactin. The blockage of dopamine receptors by antipsychotic drugs results into an increase in milk production and secretion (galactorrhea).(Ayano, 2016)

The mesocortical pathway refers to dopaminergic neurons of the ventral tegmental area that project to the frontal cortex and septohippocampal regions. These projections are thought to be involved in cognitive and emotional behaviour. Distinct levels of dopamine in the frontal cortex help in improved working memory and attention, but changes in the dopamine levels to either side can lead to memory impairment. This pathway could correlate with the negative symptoms of schizophrenia, when impaired. (Ayano, 2016)

The mesolimbic pathway is intricately linked to the reward system as dopamine forms the chemical basis of the experience of pleasure and its repeated hunt for more. The dopaminergic fibers originate in the ventral tegmental area in the midbrain and project to the amygdala, pyriform cortex, lateral septal nuclei and the nucleus accumbens. Dopamine is released after pleasurable situations and rewards the person for this activity, which stimulates one to seek out this activity more often. The same process applies to the abuse of drugs, which activates the dopamine release in the mesolimbic system. (Ayano, 2016)

The mesocortical and mesolimbic systems overlap in terms of their behavioural outcome and have similar functions. Therefore, they are collectively called the mesocorticolimbic system.

Synthesis

As it is common for catecholamines, the synthesis of dopamine begins in the liver with the production of the amino acid tyrosine out of the essential amino acid phenylalanine with the aid of the enzyme phenylalanine hydroxylase. Tyrosine is transported out of the liver to the catecholaminergic neurons in the ventral tegmental area of the substantia nigra in the midbrain and the arcuate nucleus of the hypothalamus for further processing. The enzyme tyrosine hydroxylase accelerates the attachment of a hydroxy group to tyrosine, this time-limiting reaction leads to L-Dopa, which is the last intermediate product that could pass the blood brain barrier, as dopamine itself is not capable of doing that. Dopa decarboxylase converts L-Dopa quickly into dopamine, which could now be further processed into noradrenaline and finally adrenaline. Dopamine is an intermediate product of the biosynthesis of adrenaline but has its own independent functions as a neurotransmitter.

Receptors

Dopamine carries out its functions by activating five dopamine receptors, D1, D2, D3, D4 and D5. They all belong to the large G-protein coupled receptor family and therefore have the typical 7 transmembrane domain structure. These five distinct dopamine receptors are further subdivided by their structures into the D1-like group, that consist of the D1 and D5 receptor and the D2-like group were D2, D3 and D4 belong to. The D1-like group has a larger structural homology than the D2-like group. D1 and D5 are to 50% structural identical, this is reflected in their similar affinities to a variety of dopaminergic drugs. The activation of the D1-like group by dopamine occurs via the opening of sodium channels, which is an excitatory response, or on the other hand, via the opening of potassium channels, which results into an inhibitory response. The D2-like activation leads usually to an inhibition of the target neurons (Arias-Carrián et al, 2010; Ayano, 2016) **.**

The final effect that dopamine has on his target neurons depends on which receptors are expressed and what the internal responses to the activation is. The five dopamine receptors are not equally spread in a human’s body and do all have slightly different outcomes:

The D1 receptor is the most abundant in a human nervous system and is found in high concentrations in the mesolimbic, nigrostriatal and mesocortical areas of the brain, such as the nucleus accumbens and the striatum. After knowing its preferential locations, it is not surprising that the D1 receptor is needed for voluntary movement, attention, reward, working memory and learning. Outside its functions in the central nervous system, dopamine is also known to modulate the renin levels in the kidney (Ayano, 2016).

The D2 receptor is the second most abundant receptor and is found in fairly similar brain areas. It is needed for regulating mood and emotional stability in the limbic system or movement control in the basal ganglia. The D2 receptor is especially important in terms of drug abuse and as main receptor for most antipsychotic drugs. In the periphery, the D2 receptor is present in blood vessels and can lead to vasodilation and changes in blood-pressure (Ayano, 2016).

The D3 receptor is exclusively found in the central nervous system and is mainly involved in emotion control (Ayano, 2016).

The D4 receptor is expressed in the hippocampus, amygdala, thalamus and in the hypothalamus, but it has the lowest presence of all five dopamine receptors. Its central role is the modulation of cognitive functions. The D4 receptor was also found to regulate the renal function, gastrointestinal motility, vasodilation and blood pressure (Ayano, 2016).

Processing of painful stimuli and regulation of the endocrine functions of dopamine are both controlled via the D5 dopamine receptor (Ayano, 2016).

The final effect dopamine has on its target neurons is depending on the concentrations of the different dopamine receptors, that are expressed, and can therefore have a large variety of outcomes (Arias-Carrion et al, 2010).

The reward system and its functions

The survival of a species depends on its ability to achieve the highest fitness in a particular environment Over time, only those organisms that were best able to reproduce, will prove to be superior under the forces of natural selection. But how does a certain organism know whether it is performing an evolutionarily beneficial action or not? This is the key role of the reward system, it fulfils its purpose by creating in all living organisms the desire to do actions that lead them to stay alive longer and reproduce. A species succeeds in natural selection, when it has the most advantages over another species in a given environment. To promote the best survival and reproduction strategies, the brain has evolved a reward system in order to learn, select and approach the best objectives and situations appropriate for an individual’s survival. Rewards have been adopted by the brain to tackle the challenges of evolution (Schultz, 2015).

But what are rewards actually inducing and how can they help an individual to be the fittest?

Rewards induce mainly the following three things:

Learning

Rewards are positive stimuli that are pleasurable and nice to encounter, they let the organism learn, which behaviour makes them feel good. This leads organisms to seek them more often. The rewards act as a positive reinforcer and increase the frequency of behaviour that leads to them. Rewarding stimuli can be learned with operant and classical conditioning (Arrias-Carrion et al, 2010; Schultz, 2015).

Approach behaviour and decision making

To get a mating partner or food we have to approach the object of interest. Rewards help an organism to approach more often and more confidently. There are different kinds of rewards and they induce all different combinations of feelings and emotions. Some of them we like more, others we do not like that much. We do want to get those rewards that are the most pleasurable for us and therefore we are going to make more and more decisions that help us get the desired rewards (Schultz, 2015).

Pleasure

Pleasure is an emotion that is wonderful to feel but it is only a passive experience from a reward. After a while of enjoying pleasure, we have the desire to feel this emotion even more often. Desire is an emotion that makes a behaviour purposeful and directs it towards a goal, which means that desire is an inner force that actively directs behaviour. Pleasure and desire make us perform actions that we perhaps would not consider doing without knowing in beforehand that we get a reward in the end (Arrias-Carrion et al, 2010; Schultz, 2015).

By definition, rewards have no physical properties. Instead, they are defined by the behavioural reactions they induce in an organism. Since rewards have no physical properties, no organism has specialized sensory receptors for it like for hearing, somatosensory or visual stimuli. This fact adds another level of difficulty for researchers to study reward-related behaviour, because behavioural responses are one of only few things that can be detected and investigated. But there may be a good reason why no such receptors exist. It may be much more efficient to have a neuronal system that filters out the reward components. There is a great variety of objects that could partially induce a reward, these impressions are taken up by already existing sensory receptors. The reward system combines all the different sensory inputs to one pleasurable outcome. But how does this neuronal pathway look like? (Schultz, 2015)

Anatomy reward system



Figure 1: projections of dopaminergic neurons in the reward system, Ventral tegmental area (VTA), Substantia nigra compacta (SNc), (Arias-Carrián et al., 2010)

The mesocortical and mesolimbic pathways mentioned above are suggested to contribute the most to control and to the regulation of emotion-related behaviour. The mesolimbic system includes the ventral tegmental area (VTA), that plays a crucial role in learning processes. The dopaminergic neurons of the VTA project to the nucleus accumbens. The mesocortical system connects the VTA to the prefrontal cortex. Other brain areas such as the amygdala, substantia nigra, hippocampus and hypothalamus are also thought to be involved in the reward system. The dopaminergic neurons act on either D1-like receptors or D2-like receptors to either stimulate (D1-like receptors) or to inhibit (D2-like receptors) the production of cAMP as second messenger. Dopamine is not the only neurotransmitter to play a role in the reward system, but also glutamatergic interneurons and GABAergic medium spiny neurons are present in the reward system and contribute their part to it. (Björklund & Dunnett, 2007)

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