Anandamide

Introduction

Function

Biosynthesis

Potential Usage

Sources

Glossary
**Anandamide**

**Introduction**

Our organism reacts to various chemicals found in nature but not synthesized by our body. But for what reason? The answer is simple. Our body uses signal or regulation molecules being quite similar to these natural substances. Just like the molecule this text is about.

Between 1988 and 1990 Devane, Howlett and Johnson discovered the two cannabinoid receptors CB1/CB2 at the Saint Louis University of Missouri. The cannabis substance THC binds to these receptors, so the search for the body’s own substances started shortly after.

In 1992 the Czech chemist Lumír Ondřej Hanuš and the American molecular pharmacologist William Anthony Devane discovered arachidonylethanolamide, which is commonly known as anandamide. Over the years, the two other anandamides homo-gamma-linolenylethanolamide and docosatetraenylethanolamide were found. Thus there are currently three known Anadamide derivates.

But Anandamid cannot only be found in the human body but also in cacao beans therefor in chocolate as well.

In several studies, researchers have found that are formed upon activation of pain impulses from the brain Anadamide showing an analgesic effect. Because of this effect, the endogenous cannabinoids will certainly play a significant role in the pharmaceutical treatment of pain.

**Basic informations**

- molecular formular: C22H37NO2
- density: 0,92 g/cm³
- molar mass: 347,53 g/mol
- endogenous cannabinoid
- found in chocolate and cacao beans
- Ethanolamide derivate of the arachindonic acid
- IUPAC-name: (5Z,8Z,11Z,14Z)-N-(2-hydroxyethyl)icos-5,8,11,14-tetraenamid
Anandamide

Function

Our endocannabinoid system is not made for recognition of THC but for inhibition of neuronal signals using our own cannabinoids (called endocannabinoids). Anandamide (short AEA) is one of them, binding to our cannabinoid receptors CB1 and CB2 but preferring CB1. The receptors are spreaded widely over the human organism but very concentrated in the CNS and in the brain, sitting on top of our neurons.

If an action potential arrives at the presynapse the voltage dependend Ca++ channels open up so Ca++ ions diffuse into the stroma of the respective presynapse, leading to the release of transmitter molecules, the essence of signaltransduction from neuron to neuron.

These transmitters are about to cross the synaptic gap and bind to ligand depending ion channels at the postsynapse. This causes a depolarisation and leads to a second opening of voltage depending Ca++ ion channels you can find in the membran of a postsynapse causing an Ca++ influx.

Unlike the presynaptic influx of Ca++ the postsynaptic influx activates the biosynthesis of endocannabinoids such as AEA or 2-AG using precursors sitting in the neuronal membran. The endocannabinoides are secreted by an endocannabinoid carrier system. They are not stored in vesicles such as transmitters but produced on demand.

After secretion, as an agonist, AEA binds to CB1 sitting on the presynapsis. CB1 is a g-protein linked receptor whose activation causes a blocking of Ca++ Channels, decreasing ion influx and eventually leading to a reduced release of transmitter molecules. AEAs function can be compared to a negativ feed back diluting neuronal signals.

AEA binds to potassium channels and rectifies them inwardly. In addition there are so called vanilliod receptors (TRVP1) functioning as pain modulators being activated by a couple of endogenous chemicals, one of them is Anandamide. This interaction could be used for an analgesic therapy.

Anandamide is a very lipophilic molecule, which is not like other neurotransmitters stored in vesicles and released then into the synaptic gap, but first synthesized out of precursors sitting in the membrane, and then secreted into the synaptic gap. This "on demand" mechanism is triggered by the influx of Ca ++ and activates the AEA-synthesizing enzymes. Initial of the synthesis is the depolarization of the post-synapse, resulting in a Ca ++ influx occurs and the enzyme N-acyltransferase(NAT) is enabled. This enzyme transfers of phosphatidylcholine (PC), which is linked at the C1 atom of arachidonic acid to the amino group of phosphatidylethanolamine (PE). The result is N-arachidonyl-phosphatidylethanolamine (NAPE). The last step is done by the enzyme N-arachidonyl-phosphatidylethanolamine-phospholipase D (NAPE-PLD), a phospholipase, which forms the anandamide. Inactivation of anandamide, it is a hydrolytic cleavage of Ananamidin ethanolamide and arachidonic acid. This step is catalyzed by the intracellular fatty acid amide hydrolase (FAAH).
Anandamide

Potential Usage

As an endogenous cannabinoid transmitter Anandamide has several physiological functions in our organism.
The pharmacological effect of Anandamide is the basis for a variety of research approaches during the last twenty years.
One study shows that Endocannabinoids have an emotional influence on the human organism. By blocking the hydrological degradation of Anandamide anxiety can be reduced. This result opens up an approach for studies on the medication of anxiety state or even depression. Researches have shown that psychotic and paranoid illnesses could be leveled off and even controlled by Anandamide. These diagnostic findings could open the door for a therapy of schizophrenia.
Just like read before Anandamide affects the central nervous system or the periphery. It affects the cannabanioid receptors CB1 and CB2, whereof the last one is located in the periphery and the immune system. The location of the neurotransmitters shows a connection to its particular function, which I am going to outline in these examples.
The immune system in the brain stands under the control of endocannabinoids. This fact has been scientifically proven in a rating of the Anandamide concentration, while the brain suffered damage. This release of Anandamide attracts Microglia cells, which generally negate the harm. The Endocannabinoid controls the Microglia cells in a way that the immune system cannot overreact. The research shows also, that through the influence on the endocannabinoid system, nerve cells could be protected from harmful inflammation. Therefore Anandamide is a regulation substance, which plays an important role in the controlling of Microglia cells and the determination of inflammation in nerve tissues. Regulation of the Anandamide concentration could be a potential treatment for multiple sclerosis.
Many of these CB Receptors are located in brain areas being involved in the process of cognition and thinking. Mice, which were injected with Anandamide, showed a significant behavioral difference. Their pain sensation was reduced to 80%.
Another study shows that Anandamide inhibits human breast cancer cell proliferation. Another interesting fact outlines, that Anandamide regulates the feeding behavior and the neural generation of motivation.
Anandamide

Sources

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William, Devane, Julius Axelrod - Enzymatic synthesis of anandamide, an endogenous ligand for the cannabinoid receptor, by brain membranes (1994)

Vincenzo Di Marzo - Endocannabinoid signaling in the brain: biosynthetic mechanisms in the limelight (2011)

Links

http://psychotropicon.info/amide-der-glückseligkeit/
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Glossary

Action potential

When a Neuron gets stimulated, this stimulation gets transferred via a creepage along the neurons membranes. If the stimulation gets bigger than a certain trigger point at the axon hillock the neuron gets depolarized. That means the opening of voltage dependend sodium cahnnels, which increases the sodium influx rapidly, leading again to an enhanced opening of more voltage depended channels. The membrane potential gets turned around into positive till a certain limit is reached. At this point many ion channels close again and stay inactive. Almost at the same time potassium channels are opening up causing a huge stream out of potassium ions due to the high cation concentration in the neurons stroma so the decreasing sodium influx gets compensated. Right now the stream of potassium ions directed outside is bigger than the influx of sodium ions resulting into a negative membrane potential (repolarisation). More and more potassium channels are closing or getting blocked but the continuing streaming out results into an even more negative potential than the resting potential (hyperpolarisation). The resting potential gets rebuilt by the sodium-potassium-pump. The duration of an actionpotential is around 1 ms.

Cannabinoid receptors

- agonists are substances binding to receptors and leading to their activation
- there are endogenous (body's own) and exogenous (no from our body) agonists.
- e.g. THC is an exogenous but Anandamide an endogenous agonist binding both to our cannabinoid receptors. That's why they are called cannabinoids.

Function of a G-Protein linked to CB1