Neurotransmittors compel immune-cells

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Gammabuturic-acid (GABA), glutamate and acetylcholine (ACh) are all conventionally perceived as neurotransmitters. However, their roles as mediators of other physiological systems are well established in the scientific community. A growing field of inquiry encompassing the interactions between immune cells and neurotransmitters, namely neuroimmunology, might be the most significant of these systems. This article aims to clarify 1) the intricate interactions that take place between certain white blood cells* and the formerly listed neurotransmitters and 2) this relationship in the context of disease.*

Introduction

It was demonstrated long ago that glutamate is the chief excitatory neurotransmitter in the mammalian central nervous system (CNS), meaning that glutamate increases the electrical activity in synapses*. GABA has been shown to have an opposed effect to glutamate on CNS neurons*. It, when secreted into CNS synapses, reduces nerve cell electrical activity, and hence has an inhibitory effect. Acetylcholine was the first neurotransmitter to be mapped in vertebrates. Scientists performed tests on squid axons* to elucidate both which part ACh plays and many then unknown to science precepts of neurology. ACh has an excitatory effect in CNS neurons but is also the chief neurotransmitter in neuromuscular junctions*, meaning that it is essential for the peripheral nervous systems (PNS) control of both skeletal and smooth muscles. Cells that produce or are affected by these neurotransmitters are often called GABAergic, glutamatergic and AChergic cells. The central roles of these three molecules in and outside of the brain has ben complemented by their role in many other systems including control of many white blood cells. Scientists have mostly used mouse, rat and human models to assess the inner workings of the human immune system, wherein white blood cells play a pivotal role.

The immune system is split into two domains: the innate and the adapted immune systems. The innate immune system comprises several forms of white blood cells and epithelial barriers to the environment including, among others, the skin and mucus membranes. The adaptive immune system consists of one subtype of the white blood cells, the lymphocytes. In turn the lymphocytes are divided into two subgroups: B cells and T-cells. The B cells derive their name from the organ in which they were first observed, the bursa of Fibritious, an avian organ. The T-cells name, on the other hand, is derived from were they mature, the thymus which is an organ affiliated with the immune system situated in front of the heart and behind the breastbone. Both B and T-cells originate from the bone marrow. The T-cells role in adaptive immunity is to both directly induce death to infected or cancerous cells and to, via interactions with other immune cells, regulate defensive responses to pathogens*. GABA, glutamate and ACh are all widely expressed throughout the human body, but differ in concentration between microenvironments. Scientists have established that among other tissues the pancreas, stomach, blood and extracellular brain fluid express all tree neurotransmitters. Furthermore it has been proved that both receptors* that can be activated by these molecules and enzymes* necessary for their synthesis and breakdown are widely expressed outside of the brain, therein by T lymphocytes.

* See glossary.

Biological glossary

1. **Autoimmunity**: When immune-cells attack host cells.
2. **Axons**: The conductors of the electrical signals created in neurons.
3. **Enzymes**: Proteins that catalyse chemical reactions
4. **Electrochemical potential**: The differences in electrical potential and chemical composition on either side of a membrane.
5. **Neuromuscular junctions**: The Synapse between a neuron and a muscle fibre.
6. **Neurotransmitters**: A molecule that is secreted into a synapse and binds to receptors that in turn convey a signal.
7. **Pathogens**: Are microbes or microorganisms, such as bacteria or viruses, which infiltrate a host and induce sickness.
8. **Receptors**: Proteins incorporated in the membranes of cells that convey messages by extracellular stimulus.
9. **Synapses**: The spaces between neurons into which neurotransmitters are secreted

GABAergic system in T lymphocytes

GABA is synthesised by an enzyme called GAD, transported by GAT and degraded by GABA-T. There are two different types of GABA receptors, $GABA_A$ and $GABA_B$ receptors. These work through different pathways but ultimately induce the same end result, an inhibition of CNS neurons. Scientists have demonstrated the expression of most of these components in T-cells from both humans and mice, as shown in Table 1. Furthermore scientists have also partially elucidated the role these molecules play in T-cell function. The $GABA_A$ receptor in T-cells has been extensively studied for the past decade, however both the $GABA_B$ receptors expression and physiological functions are subject for scientific inquiry as they are today undetermined. The $GABA_A$ receptors inhibition in neuronal synapses is attributed to its induction of chloride ion (Cl^-) influx into neurons. Interestingly, this effect is reversed in T-cells, i.e. $GABA_A$ receptor activation results in a Cl^- drainage in T-cells. Despite this incongruity the outcome is the same. The cells functions are down regulated, in the case of T-cells this means there proliferation plus production and secretion of signalling molecules is repressed. This discrepancy is due to the different ion and electrical potentials* in the distinctive cell types. Further inquiry has unveiled that T lymphocytes express components in the GABA metabolism, furthermore these molecules, when up regulated, have been shown to correlate with the inhibition of cell division.

Glutamatergic system in T lymphocytes

Glutamate is synthesised by the enzyme glutaminase, transported by glutamate transporter and degraded by GOT or GluD. The receptors that glutamate controls are divided into two categories termed iGluR and mGluR. These two categories are functionally distinct but both ultimately result in an excitation in neurons. The excitatory effect of iGluR in CNS is due to their direct affect on the influx of positively charged ions while the excitatory effect that follows mGluRs activation is attributed to there instigation of secondary messengers that in turn trigger neuronal excitation. Both subsets of receptors have been detected in T-cells. Fascinatingly, their effect seems to be both excitatory and inhibitory depending on extracellular ion concentrations and other factors in the immediate microenvironment surrounding T-cells. Specific subsets of the receptors have been shown to regulate T-cells connection to certain tissues and their migration. Generally they seem to effect T-cells mitosis (cell division) and secretion of signalling molecules. Scientists have as of yet not unveiled which metabolic components that are expressed by T-cells.

* See glossary.

AChergic system in T lymphocytes

ACh is synthesised by the enzyme ChAT, transported by VAChT and degraded by AChE in CNS neurons. The receptors provoked by ACh are categorized into nAChR and mAChR named after the agonists used wile discovering them, nicotine (a drug in tobacco) and muscarine (a fungal drug). nAChR excitatory effect is due to their facilitation of the influx of positively charged ions, foremost K^+ and Na^+ whereas mAChR excitatory effect is attributed to their instigation of secondary messengers. The activation of mAChRs in T-cells results mostly, depending on subtyp, in the up regulation of cell division. Certain subtypes have been shown to initiate the secretion of inflammatory agent and others have been shown to regulate signal molecule production and secretion. nAChR have been shown to down regulate certain signalling molecules and up regulate others. Scientists have much left to explore and divulge. The metabolic ACh components have all, with the exception of VAChT, been observed in T-cells and there expression has been shown to change depending on the T-cells activation state. Furthermore, in at least humans T-cells predominantly manufacture the blood ACh. This gives them a regulatory role over blood ACh, an attribute that could be manipulated to ameliorate several diseases.

Table 1: The expression and function of GABAergic, glutamatergic and AChergic components in T-cells.

Species	Components	Function
Moues	GABA, GAT, GABAT, $GABA_A$	↓Proliferation, ↓ Signalling molecule production & secretion
Human	GAT, GABAT, GAD, VIAAT, $GABA_A$	↓Proliferation
Mouse	mGluR, iGluR	↓↑Proliferation, ↓↑Signaling molecule production & secretion
Human	mGluR, iGluR[1]	↓↑Proliferation, ↓↑Connection & migration[1], ↓↑ Signalling molecule production & secretion
Mouse	mAChR	↓↑ Signalling molecule production & secretion
Human	mAChR[1], nAChR	↑ Inflamation[1], ↓↑ Proliferation, ↓↑ Signalling molecule production & secretion

Reference: Ólafsson E. 2012. Nervtransmittordrivna immunceller. Självständigt arbete i biologi, Institutionen för biologisk grundutbildning, Uppsala universitet.

GABA, Glutamate, ACh and T-cells in disease

All of the neurotransmitters discussed above are obviously involved in the regulation of T lymphocytes. This relatively newly discovered relationship is likely to have significant implications for pharmacologic treatments of many devastating diseases such as typ-1-diabetes and multiple scleroses. Typ-1-diabetes is a disease were T-cells express autoimmunity* to pancreatic cells that produce and secrete insulin. Insulin is a pivotal component in the regulation of blood glucose. This obliteration of pancreatic cells leads to hyperglycaemia, which means that blood glucose concentrations reach toxic levels. Multiple sclerosis is a condition were T-cells express autoimmunity to brain axons. The myelin sheath (a fatty protective layer around axons) is degraded which leads to neuronal cell death. Glutamate and GABA in part regulate both of these diseases. Glutamate receptors seem to

* See glossary.

control autoimmune T-cells connection and migration to the affected axon in multiple scleroses. Up regulation of GABA has been shown to entirely or partially inhibit the development of MS in a mouse mode. Furthermore, GABA has been shown to weaken autoimmune T-cells attacks on insulin secreting cells in typ-1-diabetes. ACh has been shown to affect, among others, Alzheimer's disease. Scientists showed that an increased ACh concentration in the brains extracellular fluid enhances T-cell attacks on the amyloid placks that are one of the main causes for dementia by neuronal death in Alzheimer's.

Although much has been discovered in the last decade the intricate relationship between neurotransmitters and T lymphocytes is mostly undefined and much ground has yet to be broken in this relatively new field, namely neuroimmunology. Further inquiry is required to answer the many questions that have arisen from the newly obtained understanding we today posses. With additional investigation into which GABAergic, glutamatergic and AChergic components that are expressed in immune cells and how we can manipulate them, new treatments will most likely emerge. This will fundamentally help the amelioration and possibly remedy some contemporaneous diseases.

Further reading

Bhat R, Axtell R, Mitra A, Miranda M, Lock C, Tsien RW, Steinman L. 2010. Inhibitory role for gaba in autoimmune inflammation. Proceedings of the National Academy of Sciences of the United States of America **107:** 2580-2585.

Bjurstrom H, Wang J, Ericsson I, Bengtsson M, Liu Y, Kurnar-Mendu S, Issazadeh-Navikas S, Birnir B. 2008. Gaba, a natural immunomodulator of t lymphocytes. Journal of Neuroimmunology **205**: 44-50.

Fujii T, Takada-Takatori Y, Kawashima K. 2008. Basic and clinical aspects of non-neuronal acetylcholine: Expression of an independent, non-neuronal cholinergic system in lymphocytes and its clinical significance in immunotherapy. Journal of Pharmacological Sciences **106**: 186-192.

Jin Z, Mendu SK, Birnir B. 2011. Gaba is an effective immunomodulatory molecule. Amino Acids, doi 10.1007/s00726-011-1193-7.

Levite, M. 2008. Neurotransmitters activate T-cells and elicit crucial functions via neurotransmitter receptors. Current Opinion in Pharmacology **8**: 460-471.

Meldrum BS. 2000. Glutamate as a neurotransmitter in the brain: Review of physiology and pathology. Journal of Nutrition **130:** 1007-1015.

Ólafsson E. 2012. Nervtransmittordrivna immuneceller. Självständigt arbete i biologi, kandidatprogrammet i biologi.

* See glossary.