Neurotransmitters activate T-cells and elicit crucial functions via neurotransmitter receptors
Mia Levite\(^1,2\)

Neurotransmitters are traditionally viewed as nerve-secreted molecules that trigger or inhibit neuronal functions. Yet, neurotransmitters bind also their neurotransmitter receptors in T-cells and directly activate or suppress T-cell functions. This review focuses only on the activating effects of neurotransmitters on T-cells, primarily naïve/resting cells, and covers dopamine, glutamate, serotonin, and few neuropeptides: GnRH-I, GnRH-II, substance P, somatostatin, CGRP, and neuropeptide Y. T-cells express many neurotransmitter receptors. These are regulated by TCR-activation, cytokines, or the neurotransmitters themselves, and are upregulated/downregulated in some human diseases. The context — whether the T-cells are naïve/resting or antigen/mitogen/cytokine-activated, the T-cell subset (CD4/CD8/Th1/Th2/Teff/Treg), neurotransmitter dose (low/optimal or high/excess), exact neurotransmitter receptors expressed, and the cytokine milieu — is crucial, and can determine either activation or suppression of T-cells by the same neurotransmitter. T-cells also produce many neurotransmitters. In summary, neurotransmitters activate vital T-cell functions in a direct, potent and specific manner, and may serve for communicating between the brain and the immune system to elicit an effective and orchestrated immune function, and for new therapeutic avenues, to improve T-cell eradication of cancer and infectious organisms.

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**Introduction**

It is undoubtedly clear now that many neurotransmitters can bind to their neurotransmitter receptors expressed not only in various ‘classical’ target cells within the central or peripheral nervous system, but also in T-cells, and can potently activate vital human T-cell functions needed for the T-cells to perform their specialized tasks, such as cytokine secretion, adhesion to extracellular matrix (ECM), chemotactic migration and homing into specific organs and eradication of infectious organisms and cancer cells ([1\(^*\),2,3\(*\),4\(*\),5\(*\),6\(*\),7\(*\)], most of the additional studies cited in this review, and others) (Tables 1 and 2, Figures 1–3). In fact, both activating and suppressing effects of neurotransmitters on T-cells were reported, depending on the neurotransmitter itself, as well as on all the parameters discussed below and shown schematically in Figure 4.

For maintaining clarity, brevity, and focus in this review, and because of space limitations, the present review will deal with only one type of immune cells: T-cells, and cover only the activation of these cells by certain neurotransmitters. To stay away from misleading generalizations, the review will NOT elaborate on various other effects of either the same or other neurotransmitters on diverse immune cells (such as B cells, dendritic cells, stem cells, neutrophils, macrophages, natural killer monocytes, mast), and will NOT cover the suppressive effects of some neurotransmitters on T-cell function.

Tables 1 and 2 cover for example three ‘small’ neurotransmitters: dopamine, glutamate and serotonin, and four peptidergic neurotransmitters (i.e. neuropeptides): GnRH-I, GnRH-II, Substance P, and Somatostatin and show: first, their main function in the brain; second, their known receptors in the body; third, their receptors expressed in T-cells; fourth, some of the T-cell functions these neurotransmitters (or their receptor agonists) activate, when they bind naïve/resting T-cells; and fifth, potential relevance to human disease, i.e. the reported abnormal expression of certain neurotransmitter receptors in T-cells, or the abnormal T-cell response to these neurotransmitter, reported in few human diseases.

**Neurotransmitters**

A substance is conventionally viewed as a neurotransmitter, if the following four criteria are met: first, it is synthesized in neurons; second, it is present in the presynaptic terminal and released in amounts sufficient to exert a defined action on the postsynaptic neuron or effector organs; third, when administered exogenously (as a drug) in reasonable concentrations, it precisely mimics the action of the endogenously released transmitter; and fourth, a specific mechanism exists for its removal from its site of action (the synaptic cleft).
Neurotransmitters fall into one of three chemical categories:

1. **Amino acids**: among them Glutamate, Glycine, and γ-aminobutyric acid (GABA).
2. **Biogenic amines**: among them Dopamine, Norepinephrine, Epinephrine and Serotonin.
3. **Peptidergic neurotransmitters termed neuropeptides**: among them Somatostatin, Substance P, Neuropeptide Y, Opioids, Gonadotropin releasing hormone (GnRH): GnRH-I and GnRH-II, Calcitonin gene-related peptide (CGRP), Thyrotropin releasing-hormone (TRH), Corticotropin releasing hormone (CRH), Vasoactive intestinal polypeptide (VIP), Neurotensin, Bombasin, Prolactin, Galanin, Motilin, and many others. The peptidergic neurotransmitters are well known to exert physiological effects at substantial distances from their sites of release, with clear implication for the functional interactions between nerve fibers and immune target cells.

Neurotransmitters have a very wide spectrum of activities via which they affect a kaleidoscope of body functions, some shown in Tables 1 and 2. Many neurotransmitters and/or their analogues have medicinal properties, serve as drugs for various diseases, and are subject of extensive pharmacological studies.

**Where can T-cells ‘meet’ neurotransmitters?**

T-cells may be exposed to neurotransmitters in the:

(a) **Brain** — since activated T-cells, and to a lesser extent naïve/resting T-cells, regularly transmigrate into the
**Table 2**

Four examples of neuropeptides (peptidergic neurotransmitters) that can directly activate naïve/resting human T-cells: Their primary function and receptors in the brain, receptors in T-cells, and some of their activating effects on T-cells

<table>
<thead>
<tr>
<th>Substance</th>
<th>Effects in the brain</th>
<th>Receptors in various T-cells</th>
<th>Effects on T-cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substance P</td>
<td>In CNS: regulation of mood disorders, anxiety, stress, reinforcement, neurogenesis, respiratory rhythm, neurotoxicity, nausea/emesis and pain</td>
<td>NK1, NK2, NK3</td>
<td>Stimulation of human T-cell proliferation ([50] and Payan et al., 1984); Stimulation of IL-2 production, via the NK1 receptor; Induction of atypical secretion of IL-2 and IFN-γ by Th2 antigen-specific T cell lines and clones [1**,3**]; Induction of proliferation, IL-2 production and CD4+ CD25+ and CD4+ RT1B MHC class II molecule via the NK1 receptor (Santoni et al., 2001); Injection of somatostatin into the brain homing in vivo: stimulation of efferent lymph flow and the output into efferent lymph of both small recirculating and blast lymphocytes; Increase and prolongation of in vivo CD4 T-cell output from lymph nodes, associated with a depressant effect on the output of CD8 T-cells (and B cells) (Moore et al., 1990); Enhancement of T cell adhesiveness to endothelial cells, via enhancement of LFA-1/ICAM-1 interactions and induction of T-cell chemotaxis (Vishwanath et al., 1996); Increase in T-cell proliferation by an autocrine effect of endogenous Substance P produced by T-cells; the effect is mediated by NK1 receptors (Lambrecht et al., 1999); Induction of T-cell chemotaxis, via the NK1 receptor (Hood et al., 2000); Induction of proliferation, CD25 expression and IL-2 production, and rescue of apoptosis (Santoni et al., 2002)</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>Regulates the endocrine system and affects neurotransmission and proliferation by inhibiting the release of numerous secondary hormones</td>
<td>SSTR1, SSTR2, SSTR3, SSTR4, SSTR5</td>
<td>Induction of integrin-mediated adhesion to fibronectin, [4**] and to a certain extent also to collagen type IV and laminin, via SSTR2 and SSTR3 (Talme et al., 2001); Induction of typical and atypical secretion of IL-2, IFN-γ, IL-4 and IL-10 by Th0, Th1 and Th2 antigen-specific T cell lines and clones [10**]; Induction of IL-2 secretion and proliferation [23,89]</td>
</tr>
</tbody>
</table>

CNS across the blood brain barrier, under physiological and pathological conditions.

(b) **Lymphoid organs** — as all primary and secondary lymphoid organs, among them the thymus, spleen, lymph nodes, bone marrow and gut, are massively innervated by nerves which release a variety of neurotransmitters and neuropeptides [8,9**].

Furthermore, within these lymphoid organs, there are direct contacts between nerve terminals containing neurotransmitters, and individual immune cells, among them T-cells and B-cells and mast-cells [8,9**].

(c) **Blood** — since both fenestrated and non-fenestrated blood capillaries are intensely innervated by nerve-secreting neurotransmitters, thus providing conditions for direct contacts between neurotransmitters and blood-borne T-cells in health and disease.

(d) **All the other innervated body organs** — since all these contain neurotransmitters as well as T-cells that pass through for routine immune surveillance.

Collectively, all the above indicate that various neurotransmitters may encounter and affect T-cells in everyday life, in almost every site of the body, and in almost every context of health and disease.

T-cells produce endogenous neurotransmitters and can be affected by them in an autocrine/paracrine manner

Numerous interesting and solid studies show that T-cells (and other immune cells) can in fact produce and secrete various endogenous neurotransmitters, either spontaneously or after induction by external stimuli. Some of the neurotransmitters produced by T-cells are: Dopamine,

T-cells may also be affected by some of their endogenously produced and exogenously secreted neurotransmitters in an autocrine and paracrine manner (e.g. \[10/C15/C15\]), yet only if the concentration of the respective neurotransmitter is appropriate.

Finally, I speculate that T-cells may use their own neurotransmitters not only to ‘talk’ to themselves, but also to ‘talk’ to other cells, mainly to neurons and glia cells, when they enter the brain and ‘need’ to communicate and cooperate with these CNS-resident cells, for example, during viral infection within the CNS.

T-cells express specific receptors for various neurotransmitters, and these are dynamically regulated by TCR-activation, cytokines, the neurotransmitters themselves, and other factors

Neurotransmitters exert all either excitatory or inhibitory effects on their targets by binding to their cognate receptors expressed in target cells within the nervous system. Each neurotransmitter has a broad family of receptors. The families of neurotransmitter receptors expressed in the nervous system for some of the relevant neurotransmitters and neuropeptides discussed herein, are shown in Tables 1 and 2, respectively. These tables also show the main neurotransmitter receptors expressed in T-cells, focusing primarily on published evidence for: first, the existence of these receptors at the protein level (not only mRNA, which may or may not be translated) and second, the functional response of these neurotransmitter receptors to the natural neurotransmitter itself (not only to synthetic and somewhat artificial neurotransmitter agonists).

Interestingly, the expression of the neurotransmitter receptors in T-cells seems to be very dynamic, and can change dramatically in response to different molecules and processes among them:

(a) T-cell receptor (TCR) activation. TCR-activation, that is induced naturally and specifically by viral/bacterial/parasite/cancer antigens, and can be mimicked artificially by mitogens (e.g. phorbol esters) and anti-CD3 and anti-CD28 antibodies, may dramatically affect the expression of a given neurotransmitter receptor on the T-cell membrane. For example, we recently described a striking example: the glutamate receptor of the AMPA GluR3 subtype (GluR3) is highly expressed in peripheral naïve/resting human T-cells (60–90% GluR3 positive) of all healthy individuals tested, yet eliminated completely from the T-cell surface upon TCR-activation \[11^{**}\] (Figure 2). Going deeper into the mechanism, we revealed that it is granzyme B, the key proteolytic enzyme which is routinely released from TCR-activated T-cells, that cleaves GluR3 from
such activated cells, leading to its disappearance from the cell surface for ~48 h [11**] (Figure 2).

(b) **Cytokines.** Certain cytokines, alike IL-2, can change the expression of neurotransmitter receptors in T-cells.

(c) **The neurotransmitter itself.** Alike in neurons, a neurotransmitter can regulate (usually downregulate) the expression of its own receptors in T-cells.

### Many neurotransmitters can trigger T cell function
The data accumulated thus far show that various neurotransmitters bind to their receptors in T-cells and can activate many T-cell functions in a powerful and rapid manner. **Table 1:** for dopamine, glutamate, and serotonin and **Table 2:** for the neuropeptides GnRH-I, GnRH-II, Substance P and Somatostatin (other relevant and important neuropeptides, including NPY and CGRP [3**,4*], are unfortunately not covered in this review because of space limitation) present examples of neurotransmitters that by themselves activate T-cell function. Herein, only two of these neurotransmitters will be further discussed: dopamine and glutamate.

### Dopamine
Dopamine (Table 1) is one of the principal neurotransmitters in the central nervous system involved in several
key functions such as behavior, control of movement, endocrine regulation, and cardiovascular function. The secondary lymphoid tissues are highly innervated by sympathetic nerve fibers that store dopamine at high contents, and lymphocytes also produce dopamine [12,13,14]. Dopamine signals via five different seven-transmembrane G-protein-coupled receptors termed D1–D5 dopamine receptors, some of which (particularly of the D2 subclass) represent the primary therapeutic target in a number of neuropathological disorders, including schizophrenia, Parkinson’s disease, and are expressed in Huntington Chorea.

Dopamine triggers T-cell function via its dopamine receptors

Dopamine-receptors D2, D3, D4 and D5 are expressed in T-cells ([7,10,15,16,21], see also Table 1). Furthermore, these dopaminergic receptors are genuinely functional, because various T-cell functions are affected upon binding of dopamine or dopaminergic agonists to T-cells. The T-cell features and functions activated by dopamine or by highly selective dopamine D2 and D3 receptor agonists appear in Table 1 and are shown schematically in Figure 1. For example, we revealed that dopamine on its own can activate human normal naïve peripheral T-cells and trigger their adhesion to fibronectin [10], a major glycoprotein of the extracellular matrix (ECM), via activation of 4β1 α5β1 integrin moieties. Such T-cell adhesion is critical for trafficking and extravasation of T-cells across blood vessels and tissue barriers [10].

In a subsequent confirming study, Watanabe et al. [21] found that the D3R was the predominant subtype of dopamine-receptors in the secondary lymphoid tissues and selectively expressed by naïve CD8+ T-cells from both humans and mice. Dopamine selectively induced the chemotactic migration of naïve CD8+ T-cells, and was highly synergistic with CCL19, CCL21, and CXCL12. Dopamine also selectively induced adhesion of naïve CD8+ T-cells to fibronectin and ICAM-1 by the activation of integrins. Intraperitoneal injection of mice with dopamine selectively attracted naïve CD8+ T-cells into the peritoneal cavity. Treatment of mice with a D3 antagonist reduced homing of naïve CD8+ T-cells into lymph nodes [21].

Dopamine can also induce T-cell cytokine secretion. Indeed, we found that dopamine on its own induced a significant increase in TNFα and IL-10 secretion by naïve resting normal-human T-cells, and induced ~5-fold elevation of the corresponding TNFα and IL-10 mRNA levels (without affecting IFNγ and IL-4) [7]. Interestingly, dopamine-induced TNFα upregulation was evident 24 hours after dopamine stimulation, and was mediated primarily by D3R, while IL-10 upregulation was evident after 72 hours, and was mediated prim-
Dopamine can probably also activate T-cell function indirectly, by suppressing T-regulatory cells (Treg), as suggested recently [13**,22]. Here, the endogenous catecholamines act by autocrine/paracrine loop, via dopaminergic receptors and pathways, to downregulate Treg function [13**]. The effect is mediated primarily by D1 receptors [13**].

Taken together, all the above mentioned effects, and those described in Table 1 and Figure 1, show that dopamine by itself can bind to naïve/resting peripheral T-cells, and induce T-cell adhesion, chemotactic migration, attraction and homing into specific organs, cytokine secretion, and additional T-cell functions. All these suggest that dopamine is very important not only for its well-known ‘classical’ effects (see Table 1), but also for delivering signals from the brain to T-cells, needed for effective, proper, regulated, and orchestrated immune responses.

Having said that, and focused herein only on the activating effects on dopamine on T-cell function, it should nevertheless be mentioned that dopamine can also suppress some T-cell functions and features, primarily proliferation and cytotoxicity, mainly when it interacts with activated T-cells (rather than with naïve/resting T-cells).
Relevance of the dopamine-receptors in T-cell to human diseases

Abnormal expression of dopamine-receptors in lymphocytes/T-cells, or abnormal response of dopaminergic receptors in lymphocytes/T-cells, was reported in Schizophrenia [23–25], Parkinson’s disease, [26,27], Alzheimer’s disease [17], Migraine [28], HIV [29,30], and Multiple Sclerosis [31]. Unfortunately, some of these studies studied only the presence of abnormal receptor mRNA levels rather than the functional receptor itself. Thus, further studies are needed before the pathological and pharmacological significance of these potentially exciting findings can be fully evaluated.

Glutamate

Glutamate (Table 1) is the brain’s primary excitatory neurotransmitter, involved in affective, sensory, and motor function, as well as in learning, memory, cognition, and synaptic plasticity. Glutamate signals though two broad families of glutamate receptors, consisting of the ionotropic (ion channels) glutamate-receptor, and the G-protein-coupled metabotropic glutamate-receptors. The ionotropic glutamate-receptors are subdivided into AMPA, Kainate, and NMDA glutamate-receptors, and in each, there is yet some further subdivision to individual receptors having different numbers. The metabotropic glutamate receptors are also subdivided into mGluR1 to mGluR7.

Glutamate triggers T-cell function via its glutamate-receptors

Human T-cells express several types of glutamate-receptors, and glutamate has various effects on T-cell function [32*,6*,11**,33*,34–38]. Table 1 and Figure 3 list and cite some of the glutamate-induced T-cell functions and features.

In a recent study we described for the first time, that normal human T-cells, human T-leukemia line, and the mouse anti-myelin basic protein (MBP) 87–99 T-cells (which induce experimental autoimmune encephalomyelitis (EAE), the animal model for multiple sclerosis (MS)), express very high levels of glutamate receptor GluR3 [6*]. The multiple methodologies used for showing GluR3 expression in T-cells (Figure 2a–c) include: GluR3-specific RT-PCR and sequencing, establishing identity between the T-cell GluR3 and the authentic brain GluR3, Western blot, and GluR3 cell-surface expression, as revealed by immunofluorescence-staining, flow-cytometry, and confocal microscopy [6*]. Furthermore, glutamate in the absence of any additional molecule, induced integrin-dependent adhesion to laminin and fibronectin, and chemotactic migration toward the chemokine SDF-1 [6*] (Figure 2d,e). The effects of glutamate were mimicked by AMPA (glutamate/AMPA receptor-agonist) and blocked by CNQX and NBQX (glutamate/AMPA receptor-antagonists).

Testing glutamate in a very broad concentration range, we found that glutamate-induced T-cell activation was evident in an optimal conc. of ~10 nM, which is exactly the concentrations of glutamate within the brain extracellular fluid. Taken together, the high expression of GluR3 in T-cells, and the ability of glutamate to activate T-cell functions in its physiological concentration within the brain, could be of importance in many physiological and pathological situations, among them: first, T-cell transmigration into the CNS across laminin-containing capillary endothelial cells that form the blood–brain-barrier and second, T-cell mediated autoimmune diseases, especially MS [6*].

Surprisingly, in a subsequent study [11**], we further found that the glutamate receptor GluR3 is completely eliminated from the cell surface of the TCR-activated cells, and that this is because of proteolytic cleavage of GluR3 by granzyme B released by the TCR-activated cells. This is shown schematically in Figure 2. In parallel to losing intact GluR3, TCR-activated cells also lose glutamate-induced adhesion to laminin [6*]. Thus, glutamate, via GluR3, may activate only resting, but not TCR-activated cells [6*].

Gallart et al. have recently shown that human dendritic cells undergoing maturation and in contact with T-cells, release significant amounts of glutamate, and that after productive antigen presentation, the metabotropic glutamate-receptor 1 is expressed in T-cells and mediates an enhanced T-cell proliferation, and secretion of Th1 and proinflammatory cytokines [34].

The stimulation of group I metabotropic glutamate-receptors also evokes calcium signals and c-jun and c-fos gene expression in human T-cells, thus activating multiple downstream signaling regulating important T-cell functions [38].

Glutamate, at concentrations within its normal plasma levels, and via metabotropic glutamate receptors also positively modulates the channel gating of Kv1.3 [37], a key voltage-gated potassium ion channel in T-cells [2], causing a faster current activation at significantly more hyperpolarized potentials, hence rendering the T-cells readily responsive to immune stimuli [37].

These and other glutamate-induced T-cell activating effects are mentioned in Table 1 and Figure 3.

Relevance of glutamate-receptors in T-cell to human diseases

Multiple sclerosis

Sarchielli et al. [33*] showed recently that T-cells of control subjects and MS patients express both the mRNA and the GluR3 receptor protein, in line with
T-cell-mediated autoimmune diseases, their activation phoma, or autoimmune T-cells, alike in MS and other alike cancer T-cells, that is, T-leukemia and T-lym‌pathogenicity. Body, since it would aggravate the T-cell-mediated detrimental T-cells, but this time bad for the entire ‘good’ T-cells. By contrast, if the T-cells are detrimental, as it will improve the beneficial performance of these both for the T-cells themselves and for the entire body, given neurotransmitter will most probably be beneficial the T-cells are normal and healthy, their activation by a target T-cells and the context, see Figure 4. Thus, if GluR3 expression shown previously in murine anti-MBP 87–99 T-cell line [37]. Excitingly, an upregulation of the GluR3 expression during relapse, and in patients with neuroradiological evidence of disease activity, was revealed [33*]. Furthermore, glutamate and AMPA, at concentrations of 10 nM to 10 μM enhanced T-cell proliferation to MBP and MOG, and the chemotactic migration of T-cells of both controls and MS patients. In the latter group, significantly higher proliferation values in response to glutamate were found in patients assessed during relapse and in those with gadolinium (Gd)+ enhancing lesions on MRI. Together, MS patients during relapses with evidence of disease activity on MRI, had higher GluR3 expression in their T-cells and glutamate affected these cells to a greater extent [33*]. These interesting findings are in perfect agreement with the original suggestions raised when GluR3 was first detected in encephalitogenic anti-MBP T-cells [6*], and support the idea that glutamate-induced activation of MS-associated T-cells may indeed play a vital role in this disease. This topic surely calls for further investigation.

**Autoimmune epilepsy**

We recently suggested that the cleavage of glutamate receptor GluR3 from the T-cell surface by granzyme B, upon TCR-activation, and the release of immunogenic GluR3B peptide to the extracellular milieu (especially if occurring in a continuous manner, for example in a chronic infection), could be the first step leading to the production of neuropathogenic GluR3B autoantibodies, found in some epilepsy patients (see the Discussion in [6*], the relevant Refs cited therein, and our papers on ‘Autoimmune Epilepsy’) [51].

**Are the interactions of T-cells with neurotransmitters beneficial or detrimental, first for the cells themselves and second for the overall health of the body?**

I would provocatively argue that the answer to these questions is NOT dictated by the neurotransmitter itself (which has ‘fixed’/conserved identity), but rather by the target T-cells and the context, see Figure 4. Thus, if the T-cells are normal and healthy, their activation by a given neurotransmitter will most probably be beneficial both for the T-cells themselves and for the entire body, as it will improve the beneficial performance of these ‘good’ T-cells. By contrast, if the T-cells are detrimental, alike cancer T-cells, that is, T-leukemia and T-lym‌phoma, or autoimmune T-cells, alike in MS and other T-cell-mediated autoimmune diseases, their activation by a neurotransmitter will still be beneficial for these detrimental T-cells, but this time bad for the entire body, since it would aggravate the T-cell-mediated pathogenicity. Indeed, different T-cell subpopulations often express different receptor subtypes for the same natural neurotransmitter.

**It is a matter of context: crucial factors can determine whether a given neurotransmitter would activate or rather suppress a given T-cell function**

An important take-home message from the study on the effects of neurotransmitters on T-cells, should be that a given neurotransmitter is rarely exclusively stimulatory or inhibitory, when it comes to its effects on T-cells. I would argue that the findings thus far show that often the very same neurotransmitter can be both activating and suppressing! It all depends on the absolutely crucial factors that determine the functional outcome, shown schematically in Figure 4a–f. These include:

(a) The activation state of the T-cells. Naïve/resting T-cells are often activated by a given neurotransmitter, while TCR-activated or cytokine-activated T-cells are often suppressed by the very same neurotransmitter.

(b) The subtype of neurotransmitter receptors expressed on the target T-cells. Each neurotransmitter has a broad family of receptors, which all bind the parent neurotransmitter, but respond somewhat differently, because of some different characteristics and signaling pathways. Naïve/resting T-cells often express a different composition of neurotransmitter receptors than activated T-cells [6*,33*,37,39].

(c) The neurotransmitter dose. Many neurotransmitters affect T-cell function at an optimal low dose range of ~10^{-10} to 10^{-8} M. Higher concentration may be either nonproductive, suppressive or even toxic [6*,33*,37,39].

(d) The T-cell subpopulation being stimulated. CD4+ and CD8+ T-cells may respond differently to neurotransmitters [40], and so do Th1 and Th2 cells [14,41] and regulatory and effector T-cells [13**].

(e) The cytokine, chemokine, and growth factors milieu. These may change dramatically the effect of a given neurotransmitter on a given T-cell population, as shown by published and yet unpublished data.

(f) Other neurotransmitters released concomitantly. Nerve endings often contain both a conventional neurotransmitter (such as glutamate, GABA, or dopamine) and one or more neuropeptides, as shown schematically in Figure 4e. There are many such couples of neuroactive peptides coexisting with other neurotransmitters, and specific examples are listed in the legend for Figure 4e. The neuropeptides are generally packaged in large dense-core vesicles, and the coexisting neurotransmitters in small synaptic vesicles. The location within the neuron and the
neurotransmitters activate T-cells

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release of the large and small vesicles are different. Clearly, one may envision different contexts and different outcomes: first, T-cells exposed only to one neurotransmitter or one neuropeptide; second, T-cells exposed simultaneously to a given neurotransmitter and a given neuropeptide, or to one after the other.

Each of the above parameters can dictate whether a specific neurotransmitter will activate, suppress or rather not affect at all a given T-cell function. Variations in the above parameters that define the context, are most probably the basis for some of the contradictory results reported in the literature, for example where the term ‘inhibitory neuropeptide’ was assigned to a given neuropeptide that, at physiological concentrations, can in fact activate T-cell function in a direct and profound mode.

Summary and concluding remarks

The large body of evidence outlined in this review indicates that some of the ‘classical’ neurotransmitters, alike dopamine, glutamate and serotonin, and numerous neuropeptides among them Substance P, GnRH-I and II, Neuropeptide Y, CGRP and Somatostatin have the ability to bind to their cognate receptors in T-cells and activate pivotal T-cells functions.

Among the T-cell functions and features that are triggered/elevated by neurotransmitters (see Tables 1 and 2 and Figures 1 and 3) are: T-cell adhesion, chemotactic migration, homing into solid organs, cytokine secretion, proliferation, cytotoxicity, ion currents, the levels of intracellular Ca²⁺, the level of surface expressed receptors, de novo gene expression, mRNA levels of various proteins, signal transduction, and others. The expression of the neurotransmitter receptors in T-cells is by no means constant: it can be changed dramatically by TCR-activation, cytokines, the neurotransmitter itself, other co-released neurotransmitters and additional factors. T-cells also produce and secrete some neurotransmitters and may be affected by them in return, by an autocrine/paracrine mode. Abnormal levels of neurotransmitter receptors in T-cells have been observed in a few human diseases. If these interesting findings would be reproduced and extended in future studies, it could mean that perturbed interactions between neurotransmitters and T-cells, for example due to too high or low level of neurotransmitter receptors in T-cells, or due to mal function of the brain because of chronic stress or injury, play an active role in the pathogenesis of the respective diseases, or in the T-cell’s effort to fight the disease.

In conclusion, neurotransmitters may be as important for the immune system as for the nervous system, and as such deserve every effort to learn more how they affect T-cells, where and when. In addition, the direct, rapid, potent, specific, and receptor-mediated manner by which certain natural neurotransmitters activate T-cells and improve their function in vitro and in vivo, also opens up novel and safe ways by which the pharmacological world could take advantage of it to fight some human diseases, primarily cancer and infectious diseases. Indeed, an especially attractive therapeutic avenue is to activate T-cells by natural neurotransmitters ex vivo, for improved adoptive T-cells immunotherapy of cancer. We are currently moving forward to test this exciting therapeutic option.

Acknowledgements

I thank Yonatan Ganor for his contribution to the preparation of the tables.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

• of special interest
•• of outstanding interest


This is the first review summarizing and discussing a completely novel concept: neurotransmitters can activate T-cells in a direct and powerful manner and trigger key T-cell functions. Neurotransmitters do so by stimulating their cognate functional receptors expressed in T-cells.


This study reveals a very surprising and unique phenomenon: neuropeptides can on their own trigger cytokine secretion by Th1 and Th2 cells, and even induce a ‘forbidden’ atypical cytokine secretion by already committed Th1 and Th2 cells e.g. IFNγ and IL-2 secretion by Th2 clones, and IL-4 secretion by Th1 clones. This unique property of neuropeptides may have wide implications to diseases that are mediated by Th1 cytokines and that can be arrested by a shift to Th2 cytokines, or visa versa.


A study showing that key neuropeptides: somatostatin, Neuropeptide Y, and CGRP can directly activate T-cells and induce their adhesion to glycoproteins of the extra cellular matrix. Substance P and some of its fragments have a completely opposite inhibitory effect on T-cell adhesion. The study also shows the neuropeptide receptors mediating the effects of these neuropeptides on T-cells.


This study is the first evidence that the neuropeptides GnRH-II and GnRH-I can each on its own trigger several human T-cell functions, among them de novo gene expression of a key laminin receptor, adhesion to laminin, chemotactic migration, and homing in vivo into selected organs. The study also shows that T-cells produce the neuropeptides GnRH-I and GnRH-II.


This is the first evidence for high glutamate receptor GluR3 cell surface expression in normal and EAE-inducing anti-MBP T-cells, and that glutamate or AMPA agonists, at a low 10 nM concentration, can activate T-cells and induce their adhesion and migration. The relevance of glutamate-induced T-cell activation to multiple sclerosis (and other T-cell mediated diseases) is suggested and discussed.
7. Besser MJ, Ganor Y, Levine M: Dopamine by itself activates either D2, D3 or D1/D5 dopaminergic receptors in normal human T-cells and triggers the selective secretion of either IL-10, TNFα or both. J Neuroimmunol 2005, 169:161-171. This study shows that dopamine on its own triggers secretion of IL-10 and TNFα by normal human T-cells, and that it does so by activating different dopaminergic receptors expressed in these cells. This exclusive dopamine-induced secretion of either the anti-inflammatory IL-10, or the pro-inflammatory TNFα, differs markedly from the classical TCR-induced non-selective cytokine secretion and as such may have wide implications.


9. Weine E, Nohr D, Michels S, Muller S, Zentel HJ, Fink T, Krekel J: Molecular anatomy of the neuro-immune connection. Int J Neurosci 1991, 59:1-22. A very exiting, important and comprehensive study, showing the presence, distribution, and coexistence of various peptides, neuroendocrine markers and enzymes of the catecholamine pathway in nerves supplying many lymphoid tissues in a variety of mammalian species. The possible importance to various diseases is discussed.

10. Levine M, Chowers Y, Ganor Y, Besser M, Hershkovits R, Cahalon L: Dopamine interacts directly with its D3 and D2 receptors on normal human T cells, and activates beta 1 integrin function. Eur J Immunol 2001, 31:3504-3512. The study shows that dopamine by itself activates naive/resting human peripheral T-cells. Dopaminergic D2 and D3 receptors expressed in these cells. This also reveals the dose range in which dopamine can activate resting naive T-cells.


12. Bergquist J, Tarkowski A, Ekman R, Ewing A: Dopamine-induced non-selective cytokine secretion and as such may have wide implications.


28. Sarchielli P, Di Filippo M, Candelieri A, Chiarisieri D, Mattioni A, Tenagle S, Bonucci M, Calabrese P: Expression of ionotropic glutamate receptor GluR3 and expression of glutamate on MBP- and MOG-specific lymphocyte activation and chemotactic migration in multiple sclerosis patients. J Neuroimmunol 2007, 188:146-158. A study showing the expression of glutamate receptors AMPA GluR3 in T-cells of healthy individuals and in patients with multiple sclerosis. The study also shows higher GluR3 expression and higher activating effect of glutamate on T cells of MS patients during relapses and with evidence of...
disease activity on MRI. These observations support the notion that glutamate-activation of autoaggressive T-cells can contribute to the pathology of MS.


An important study reporting that naive T cells predominantly express the serotonin receptor 5-HTR, that 5-HTR expression is substantially enhanced on T-cell activation (which leads to the expression of the 5-HT(1B) and 5-HT(2A) receptors), and that exogenous 5-HT induces rapid phosphorylation of ERK1/2 and IkappaBalpha in naive T cells.


