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Direct interactions between the nervous system and the immune system

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The major aim of my research is to elucidate the mechanisms by which the nervous system can directly affect the function of the immune system. As a first step toward this goal, I am investigating whether neurotransmitters, through their specific receptors, can induce or modulate various T cell functions (Figure 1). Special emphasis is put on the specific ion channels involved, and on the signal transduction pathways underlying such direct neuro-immuno interactions. In addition, I am investigating whether T cells, alike neurons, can be electrically excited by neurotransmitters, and whether they can be induced to function in a non-conventional immunological manner, i.e. by modulating their membrane potential.

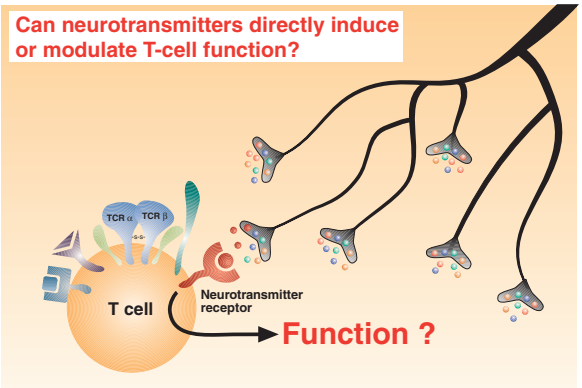

Fig. 1. *Can neurotransmitters, through their specific receptors, 'talk' directly to T cells ?*

I am also interested in studying the direct and non-conventional immunological effects of autoimmune lymphocytes on the function of the nervous system under pathological conditions. Specifically, I am investigating whether autoantibodies to the GluR3 subtype of glutamate receptor can be responsible for the neuronal death, brain pathology, and epilepsy observed in some human epileptic diseases (especially Rasmussen's Encephalitis [RE]), and if so, by which mechanism(s) (Figure 2).

I approach my two research topics at the supracellular, cellular, and subcellular levels, in a multidisciplinary manner, using immunological, biochemical and electrophysiological methodologies.

So far, the most salient findings of my research are as follows:

1. The direct interaction of neurotronsmitrers with their cognate receptors expressed in T cells triggers various T cell functions:

A. Neurotronsmitrers, by direct interaction with T cells, induce the secretion of cytokines, and abrogate their commitment to a distinct Th1 or Th2 phenotype.

B. Neurotronsmitrers, through their specific receptors, activate specific integrin moieties on the T cell surface, resulting in adhesion to extracellular matrix (ECM) components.

C. Neurotronsmitrers can dictate the pathogenicity of encephalitogenic T cells (i.e. of T cells inducing experimental autoimmune encephalitis - EAE), through direct and short-term interactions.

2. The T cell voltage-gated potassium channel plays a pivotal role as an on/off switch of β1 integrin activation:

A. The T cell voltage-gated potassium channel (the Kv1.3 channel) is the principal 'decision-making element' for β1 integrin-mediated activation and function: Opening the channel leads to integrin activation, whereas blocking prevents it.

B. The Kv1.3 channel serves as a common merging step, through which various stimulatory and inhibitory physiological effectors affect the T cell β1 integrins.

C. The T cell Kv1.3 channels and β1 integrins co-immunoprecipitate, and are thus physically associated. This may allow them to directly communicate with one another, and may underlie their tight functional cooperation.

3. An increased concentration of extracellular K^+ ions triggers the activarim of T cell integrins.

An elevated level of extracellular K^+ ions ($[K^+]_O$), is by itself a sufficient trigger to activate T cell β1 integrin moieties, adhesion to ECM components, and migration. Such increased concentration of $[K^+]_O$ is characteristic of injured, stressed and even normal (neurotransmier-stimulated) conditions. Increased $[K^+]_O$ exerts its activating effect by depolarizing the T cells and by opening their Kv1.3 channels. These findings suggest a mechanism, not known thus far, by which T cells can be rapidly activated and recruited (especially by the nervous system)

when needed, in a non-conventional immunological manner.

4. Dopamine, through its D3 receptor, depolorises T cells, triggers their β1 integrin function, and dictates their *in vivo* behavior.

A. A functional dopamine D3 receptor is expressed in normal human and mouse T cells.

B. Direct activation of the dopamine D3 receptor depolarizes T cells (i.e. causes a positive shift of the membrane potential), and triggers their proliferation and integrin function.

C. The *in vivo* behavior of EAE or DTH-inducing T cells is markedly modified after direct and brief stimulation of the dopamine D3 receptor.

These findings suggest an important role for dopamine in regulating T cell function under physiological and pathological conditions.

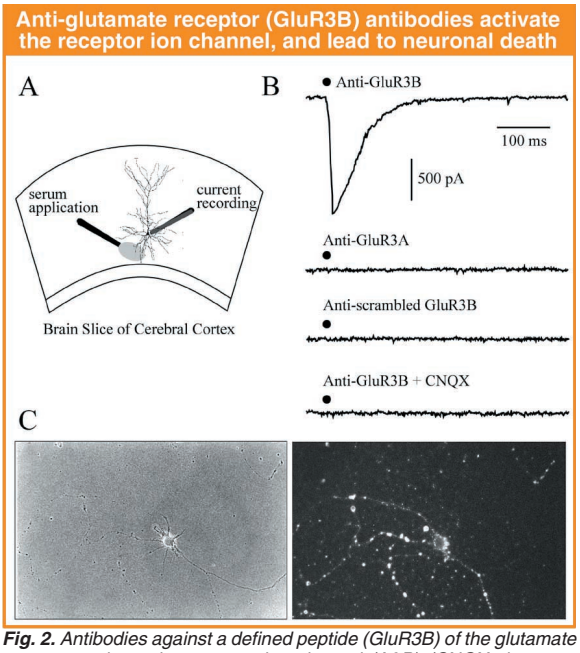

Fig. 2. *Antibodies against a defined peptide (GluR3B) of the glutamate receptor activate the receptor ion channel (A&B) (CNQX-glutamate receptor antagonist), and kill hippocampal neurons (C), as indicated by phase contrast micrographs (C left) and fluorescence micrographs of Annexin V binding (C right), taken following short incubation with these antibodies.*

5. Autoantibodies to a specific epitope of the glutamate receptor (GluR3B) kill neurons by activation of the receptor ion channel, and cause brain pathology.

A. Antibodies to a particular epitope of the GluR3 subtype of the glutamate receptor (the GluR3B peptide), found in patients suffering from RE, bind, depolarize and kill neurons in a complement-independent manner (Fig. 2).

B. The anti-glutamate receptor antibodies kill neurons by an excitotoxic mechanism, i.e. over-activation of glutamate receptors. Such a pathogenic mechanism is exerted under neurodegenerative conditions by excess glutamate. (Fig 2)

C. In mice, anti-GluR3B antibodies cause multiple (RE-like) brain pathology but not epilepsy.

Taken together, these findings indicate that autoimmune lymphocytes may contribute to the etiology of the human neurological epileptic disease: RE. Moreover, these observations shed light on a novel mechanism by which autoantibodies can lead to neuronal damage (i.e. over-activation of a neurotransmitter receptor).

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