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Meeting abstract

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Impact of norepinephrine, dopamine and substance P on the activation and function of CD8 lymphocytes

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During the past 30 years in became evident that neurotransmitter are important regulators of the immune system. The presence of nerve fibers and the release of neurotransmitters within lymphoid organs represents a mechanism by which signals from the central nervous system influence the immune cell functions. Neurotransmitter per se cannot induce any new function in immune cells but they are mainly responsible for the "fine-tuning" of an immune response. There is already a broad knowledge on the influence of neurotransmitter on B cells or CD4 lymphocytes/T helper cells, but with regard to CD8 positive cytotoxic T lymphocytes (CTLs) there are still many open questions. Therefore, we conducted the present study in order to complement the picture of neurotransmitter action on this leukocyte subset. We investigated the influence of norepinephrine, dopamine and substance P on the key functions of CTLs in vitro: activation, extravasation, migration and cytotoxicity. The activation of CTLs via CD3/CD28 cross-linking was inhibited by all of the three investigated neurotransmitters via mechanisms that involve PKA as investigated by the use of specific cAMP analoga. Furthermore, these cells showed a decrease in ERK1/2 phosphorylation and their level of IL-2 mRNA was reduced. Addition of high dose IL-2 was able to reverse the inhibiting effect of the neurotransmitters. With regard to extravasation we found dopamine to be a strong inducer of the adhesion of naïve CD8 lymphocytes to endothelium. In contrast, norepinephrine induced the adhesion of activated/effector T cells. Norepinephrine increases the IL-8 release from endothelium thereby leading to an increased adhesion of CXCR1 positive cells. We found CXCR1 to be mainly expressed on activated, perforin positive CTLs. All of the investigated neurotransmitter increased the spontaneous migratory activity of naïve CTLs with dopamine being the strongest inducer. But activated CTLs showed a reduced migratory activity in the presence of norepinephrine and substance P which seems to be mediated via the Epac/Rap1 pathway as investigated by the use of specific cAMP analoga. Dopamine had no effect on activated CTLs since dopamine receptors are down-regulated during the activation process. The ability of activated CTLs to release their cytotoxic granula in response to CD3 cross-linking was analyzed by measuring the beta-hexosamidase release. This process was not influenced by any of the neurotransmitters used. In conclusion, there is no general scheme for neurotransmitters to act either stimulatory or inhibitory on leukocytes. In contrast, the effect of a neurotransmitter depends on the leukocyte subtype and its activation state or phenotype. Thus, neurotransmitters are specific modulators of certain immune functions.

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