Interleukin -7 (IL-7) Increases Metabolic Thymic and CNS Activity

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Keywords: Interleukin-7; Non-Human-Primate; Immune-reconstitution; T-cells; Immunotherapy

Letter to the Editor

Interleukin-7 (IL-7) is currently used in a number of clinical trials in humans, including treatment trials for patients with HIV or HCV infection [1]. We would like to draw the attention concerning the impact of IL-7 on the central nervous system (CNS), since most clinical evaluations may not include detailed CNS examination, e.g. Positron Emission Tomography - Computed Tomography (PET-CT) or the evaluation of changes in complex behavior patterns.

IL-7, a pleiotropic cytokine, is predominantly produced by non-lymphoid cells, it protects T-cells from apoptosis and orchestrates T-cell receptor (TCR) rearrangement [2]. Patients with lymphopenia, either induced by chemotherapy or as consequence of hematopoietic stem cell transplantation (HSCT), show high levels of IL-7 [3,4]. IL-7 may aid to restore thymic function, yet rather associated with the preferential accumulation of recent thymic emigrants in lymph nodes [5].

Theoretically, a broader TCR repertoire may provide TCRs capable of recognizing tumor-associated antigens, it may also aid to more effectively fight off viral infections after HSCT. Administration of recombinant IL-7 into mice suggested that the peripheral accumulation of T cell receptor excision circles (TRECs) is not due to increased thymic activity, yet rather associated with the preferential accumulation of recent thymic emigrants in lymph nodes [5].

Other studies appreciated IL-7 effects on non-lymphoid tissues which suggested a broader role of this cytokine in human physiology: IL-7 is able to drive differentiation of human neuronal progenitor cells [7]. The notion that IL-7 affects the CNS was further substantiated by the demonstration that IL-7 leads to signaling in the hypothalamic arcuate nucleus (ARC) affecting hypothalamic body weight regulation along with the modulation of neuropeptides that control food intake [8]. These data warranted more detailed examination of IL-7 effects in a non-human primate (NHP) model to revisit IL-7 mediated effects on metabolic organ specific activity (Figure 1a-d).

We tested whether recombinant IL-7 (rIL-7) affects thymic and CNS metabolic activity by injecting rIL-7 into four female non-human primates (NHPs) (Macaca mulatta) of chinese origin, 3 years of age, body weight: 4.4 – 5.8 kg, all females (Figure 1a,b and Supplementary material S1). NHPs were injected four times, every 72 hrs with 100 µg rIL-7/kg bodyweight s.c. (Figure 1c). Two NHPs (females, 3 years of age, body weight: 4.4 – 5.2 kg) received only the rIL-7 diluent as a control. Immunophenotyping of NHP peripheral blood mononuclear cells, constitutive and IL-7-induced STAT-5 phosphorylation (Supplementary Figure 1A-D), glucose, C-reactive protein (CRP), hormones adrenocorticotropic hormone [ACTH], cortisol and liver transaminases (Supplementary Table S1) were measured longitudinally. Only NHPs (4/4) who received rIL-7 showed a drop in CD4+ and CD8+ T-cells after the first rIL-7 injection (Figure 1d, Supplementary Figure S1A), yet we could not detect differences in constitutive and IL-7-induced STAT-5 phosphorylation (Supplementary Figure S1B) nor in IL-7 receptor (IL-7R) density or cell numbers in CD4+ and CD8+ T-cells (Supplementary Figure S1C). Concomitant with the drop of the absolute numbers of CD4+ and CD8+ T-cells (Supplementary Figure S1A), we observed in 2/4 animals a decreased percentage of CD4+ T cells in and an increased percentage of double negative (CD3-/+)CD4-CD8- cells in the lymphocyte compartment (Figure 1d, Supplementary Figure S1D). A F-18 fluorodeoxyglucose (FDG) FDG PET-CT was performed 24 hrs prior to the first and 8 hrs after the last (i.e. the fourth) rIL-7 injection (Figure 1c and representative raw data in Supplementary Figure S2A) and in control NHPs (average injected radioactivity: 6.36 ± 0.37 MBq/kg). The mean standard uptake values (SUV) are provided in Supplementary Figure S2B. 2/4 NHPs after rIL-7 application exhibited increased thymic glucose metabolic rates (Supplementary Figures S2A and S2B) and increased bone marrow activity, 3/4 NHPs exhibited increased CNS metabolic activity (Supplementary Figure S2B and the Supplementary Movie Files SM1SA, before and SM1SB after rIL-7 injection of animal ID 6026). We did not observe differences in liver activity before and after rIL-7 injection or differences between animals with IL-7 or saline (control) injection. Also the plasma levels of the liver enzymes alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, and C-reactive protein of age, body weight: 4.4 – 5.8 kg, all females (Figure 1a,b and Supplementary material S1).
protein did not differ before and after rIL-7 injection, nor between animals with or without IL-7 injections (Supplementary Table S1). Similarly, ACTH (the main regulator of cortisol production), cortisol (involved on neoglucogenesis) and glucose levels did not change upon IL-7 treatment (Supplementary Table S1).

The lack of FDG uptake in the study published from Sportes and co-workers [6] may most likely be linked with the older age of the study participants, the underlying malignant disease or a lack of viable thymic resources. Younger age, as in the NHPs in the current report, may be associated with viable thymic resources and subsequently increased thymic metabolism.

IL-7 injection in NHPs was shown to induce naïve CD4+ and CD8+ T-cells to acquire a memory-like phenotype [9], and IL-7 injection in mice has been shown to upregulate CD8 expression [10]. Increased levels of double negative (CD3-/+)CD4-CD8- T-lymphocytes in NHPs after IL-7 treatment has not been reported up to now, the mechanism remains to be elucidated. One of the NHPs who exhibited increased levels of double negative CD3-/+CD4-CD8- T-cells after IL-7 injection has not been reported up to now, the mechanism remains to be elucidated. One of the NHPs who exhibited increased levels of double negative CD3-/+CD4-CD8- T-cells after IL-7 injection has not been reported up to now, the mechanism remains to be elucidated.

Increased IL-7-mediated thymic activity demonstrates that viable thymic tissue can be activated in younger individuals; we observed also increased metabolic activity in bone marrow. This has also been observed in clinical studies with individuals who received 30 and 60 µg IL-7 /kg bodyweight leading to increased B-cell progenitors, yet without increased numbers of peripheral B-cells [6]. In summary, our results suggest that IL-7 is able to activate thymic tissue, if functionally receptive. Increased CNS metabolic activity after IL-7 application suggests to monitor the effects of IL-7 for more complex neurological functions and the CNS-metabolic axis in more controlled, comprehensive study settings. It also prepares to consider effects of cytokines on networks of non-lymphoid cells and tissues in patients enrolled in IL-7 trials.

Acknowledgement

The work was supported from a grant from SIDA, the Söderberg Foundation and VR, Sweden, to Markus J. Maeurer.

References