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Research paper

Ventromedial hypothalamic lesions downregulate multiple immune signaling pathways in rat pancreatic islets

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HIGHLIGHTS

- VMH lesions change the expression of immune responses genes in rat pancreatic islets.
- VMH lesions downregulated multiple immune signaling pathways in rat pancreatic islets.
- The molecular pathways in upregulated genes families were not detected after VMH lesions.

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ABSTRACT

It was recently reported that ventromedial hypothalamic lesions change the expression of cell proliferation-related genes and metabolism-related genes in rat pancreatic islets. This study has examined how gene families involved in immune responses are regulated in rat pancreatic islets after VMH lesions formation. Total pancreatic islets RNA was extracted, and differences in the gene expression profiles between rats at day 3 after VMH lesioning and sham-VMH-lesioned rats were investigated using DNA microarray and real-time polymerase chain reaction. VMH lesions downregulated multiple immune signaling pathways in rat pancreatic islets. Real-time polymerase chain reaction also confirmed that gene expressions of RT1 class II, locus Bb (RT1-Bb) was up-regulated and Spi-B transcription factor (Spib) was downregulated at day 3 after the VMH lesions. Ventromedial hypothalamic lesions may change the expression of multiple immune response genes in rat pancreatic islets.

1. Introduction

Over the past 20 years, the functional autonomy of both the immune and central nervous systems has been successfully challenged. Although the ventromedial hypothalamus (VMH) is one of the centers of parasympathetic nervous system, to date, there has been little reported regarding the role of the hypothalamus in directly changing the expression of immune response genes [1].

According to Okamoto et al. [2], acute (30 min) electrical stimulation of the VMH caused a remarkable decrease in the mitogenic response of splenic lymphocytes to Concanavalin A, which is a plant mitogen, and is known for its ability to stimulate mouse T-cell subsets in rats [3]. The authors emphasized that this immunosuppressive effect is mediated through the activation of the sympathetic nerves via the beta-adrenergic pathway. Moreover, Kaname et al. [4] reported that VMH electrical stimulation, which elicits threat behaviors, induced granulocytosis and lymphopenia, including CD4+ and CD8+ cells, the decrease in the surface expression of CD62L on CD4+ and CD8+ cells or granulocytes which were concomitant with elevations of plasma cortisol, epinephrine and norepinephrine levels in the peripheral blood in cats. Moreover, the results obtained indicate that chronic electrical stimulation of the VMH decreases cell-mediated immune response, represented by NK cell activity [5]. Recently, it has been reported that VMH lesions can directly change the expression of immune response gene families [1]. Also, we previously reviewed focuses on the relationships between the VMH and the expressions of immune response genes [1].

Abbreviations: cDNA, complementary DNA; DAVID, database for annotation,visualization, and integrated discovery; PCR, polymerase chain reaction; RTI-Bb, RT1 class II, locus Bb; Spib, Spi-B transcription factor; VMH, ventromedial hypothalamus.

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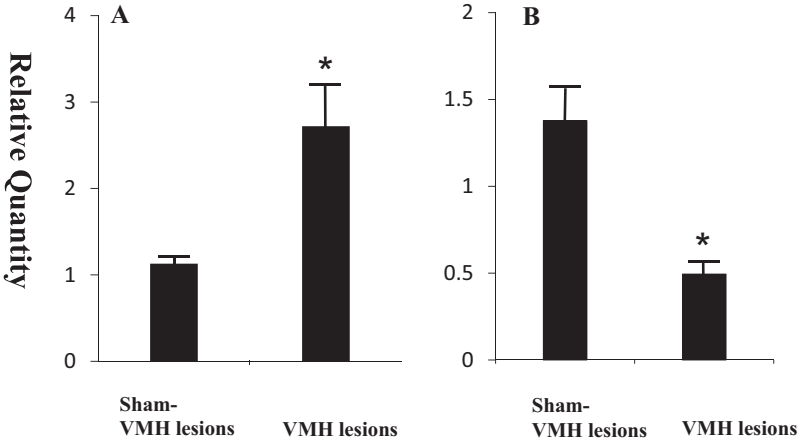

Fig.1. Ventromedial hypothalamic lesion-induced gene expression in the real-time PCR analysis. The real-time PCR analysis of total RNA extracts was described in materials and methods. A, RT1-Bb, B, Spib. Values are the means ± SE of different experiments. $^{*}P < 0.05$, compared with the sham-VMH-lesioned rats.

We previously reported that VMH lesions stimulated cell proliferation of rat pancreatic islet B and acinar cells primarily through a cholinergic receptor mechanism [6], and changed the expression of cell proliferation-related genes [7] and metabolism-related genes in rat pancreatic islets [8]. DNA microarray analysis is a powerful tool for detecting the characterization of the messenger RNA (mRNA) expression pattern of a large number of genes. In the present study, we used DNA microarray analysis to identify multiple immune response genes for which expression profiles showed significant modulation and to investigate the cellular mechanisms

Table 1
Main functional enrichment results of the interaction network in downregulated (>2-Fold) genes in pancreatic islets after VMH lesioning.

GO Term	Description	Genes	*P*-value
0002684	Positive regulation of immune system process	Bcl2a1d, Cd19, Cd3e, Cd37, Cd38, Cd28, Cd4 Cd69, Cd74, Cd79b, Fcer1g, Fcer2, Fcgr2b, RT1-Ba, Sash3, Cxcl10, C1qc, C1qb, C3, C6, Cfp, Coro1a, Hspa1b, RT1-Da, Itgal, Il2rg, Il6, Il7r, Irak3, Klrk1, Lax1, RT1-DMa, Mmp9, Nfkbia, Ptpn22, Ptprc, C1s, Lck, Syk, Tlr7, Tgfb2, Tgfbr2, Tnfrsf13c, Vcam1	5.3E-27
0050778	Positive regulation of immune response	Bcl2a1d, Cd19, Cd3e, Cd28, Cd69, Cd79b, Fcer1g, Fcer2, Fcgr2b, RT1-Ba, Sash3, Alb, Ccl5, Cxcl10, Cxcl12, Cxcl9 C1qc, C1qb, C3, C6, Cfp, Fabp4, Hspa1b, RT1-Da, Il6 Klrk1, Lax1, RT1-DMa, Nfkbia, Pla2g4a, Ptpn22, Ptprc, C1s, Lck, Syk, Tlr7, Tgfb2, Tgm2, Tnfrsf13c	1.5E-20
0006955	Immune response	Btla, Btk, Cd28, Cd4, Cd69, Cd74, Faim3, Fcer1g, Fcgr2b, Gpr183, RT1-Ba, Sp100, Swap70, Ccl2, Ccl21b, Ccl24, Ccl3, Ccl4, Ccl5, Ccl6, Ccl7, Ccr2, Cxcl1, Cxcl10, Cxcl12, Cxcl13, Cxcl2, Cxcl9, C1qc, C1qb, C3, C6, Cfp, Cybb, Gbp5, RT1-Da, Itgal, Irf8, Il1rl1, Il2rg, Il6, Il7r, Lax1, Ltb, RT1-DMa, RT1-DMb, Ptprc, C1s, Tlr7, Tgfbr3	2.4E-20
0045321	Leukocyte activation	Bcl2a1d, Blnk, Btk, Cd3e, Cd28, Cd4, Cd48, Cd74, Fcer1g, Fcgr2b, Gpr183, Swap70, Cxcl12, Cxcr4, Cr2, Coro1a, Dpp4, Itgal, Itgb2, Irf1, Il7r, Klrk1, Lcp2, Lax1, RT1-DMa, Ptpn22, Ptprc, Lck, Syk, Tlr7, Tgfbr2	4.0E-15
0002253	Activation of immune response	Bcl2a1d, Cd19, Cd3e, Cd69, Cd79b, Fcer1g, C1qc, C1qb, C3, C6, Cfp, Klrk1, Lax1, Nfkbia, Ptpn22, Ptprc, C1s, Lck, Syk, Tlr7	8.2E-15
0042379	Chemokine receptor binding	Ccl2, Ccl21b, Ccl24, Ccl3, Ccl4, Ccl5, Ccl6, Ccl7, Ccr2, Cxcl1, Cxcl10, Cxcl12, Cxcl13, Cxcl2, Cxcl9	1.6E-14
0008009	Chemokine activity	Ccl2, Ccl21b, Ccl24, Ccl3, Ccl4, Ccl5, Ccl6, Ccl7, Cxcl1, Cxcl10, Cxcl12, Cxcl13, Cxcl2, Cxcl9	2.8E-13
0046649	Lymphocyte activation	Bcl2a1d, Blnk, Cd3e, Cd28, Cd4, Cd48, Cd74, Gpr183, Swap70, Cxcl12, Cxcr4, Cr2, Coro1a, Dpp4, Itgal, Itgb2, Irf1, Il7r, Klrk1, Lax1, Ptpn22, Ptprc, Lck, Syk	1.2E-12
0050870	Positive regulation of T cell activation	Cd3e, Cd28, Cd4, Cd74, RT1-Ba, Sash3, Coro1a, Itgal, Il2rg, Il6, Il7r, RT1-DMa, Ptprc, Lck, Syk, Tgfbr2, Tnfrsf13c, Vcam1	3.3E-12
0002696	Positive regulation of leukocyte activation	Cd3e, Cd38, Cd28, Cd4, Cd74, Fcer1g, RT1-Ba, Sash3, Coro1a, Itgal, Il2rg, Il6, Il7r, RT1-DMa, Ptprc, Lck, Syk, Tgfbr2, Tnfrsf13c, Vcam1	2.4E-11