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Adrenomedullary Response to Glucagon in Patients with Primary Sjögren's Syndrome

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Abstract

Several studies showed signs of autonomic dysfunction in patients with primary Sjögren's syndrome (pSS). Adrenomedullary function might be of importance for pSS pathogenesis by affecting salivary gland functions and modulating immune responses. The aim of the study was to evaluate the adrenomedullary hormonal system in patients with pSS.

The glucagon test (1 mg i.v.) was performed in 18 pSS patients and 13 control subjects. During the testing each patient had electrocardiographic and impedance cardiographic monitoring. Plasma epinephrine and norepinephrine were assayed by liquid chromatography with electrochemical detection after batch alumina extraction.

Baseline concentrations of epinephrine and norepinephrine were comparable between pSS and controls. Glucagon administration induced a significant increase in systolic blood pressure, diastolic blood pressure, heart rate, cardiac output ($p < 0.01$), stroke volume; however the changes were comparable between pSS and controls. Epinephrine levels increased ($p < 0.01$) in response to glucagon administration while norepinephrine concentration did not change. There was no significant difference in neurochemical responses to glucagon between pSS and controls. In conclusion, the present results suggest normal adrenomedullary function in pSS.

Keywords

Primary Sjögren's syndrome; epinephrine; adrenal medulla; norepinephrine

Introduction

Primary Sjögren's syndrome (pSS) is an autoimmune disease affecting predominantly exocrine glands such as salivary and lacrimal glands as well as non-exocrine tissues. Autoimmune destruction of the exocrine glands has been considered the main mechanism in the pSS pathogenesis; however, discordant findings between degree of glandular hypofunction and histologically proved destruction of the glands indicate additional mechanisms of the pSS pathology. It has been suggested that the glandular hypofunction could be partly caused by an interference with nervous signaling to the glands. (Humphreys-

Beher et al. 1999; Dawson et al. 2006) Several studies showed signs of autonomic dysfunction in pSS.(Mandl et al. ; Mori et al. 2005; Sakakibara et al. 2004; Mandl et al. 2007)

Epinephrine secreted from the adrenal medulla together with norepinephrine released locally by sympathetic nerve endings affect the volume, rate of secretion and composition of saliva. Catecholamines were also found to influence immune functions in particular T cells and monocytes by means of adrenergic receptors.(Torres et al. 2005; Wahle et al. 2005; Takahashi et al. 2004) Elenkov and his coworkers found that basal epinephrine level conditions cytokine responsiveness of immune cells. The authors also suggested that hypo- or hyperactive adrenal medullas in some individuals may shape opposite cytokine profiles. (Elenkov et al. 2008) Salivary secretion of IgA, an antibody increased in Sjögren's syndrome, has also been found to be modulated by epinephrine.(Cox et al. 2007) Therefore, adrenomedullary function may be of importance for pSS pathogenesis by affecting salivary gland functions and modulating immune responses.

As far as we know, adrenomedullary function has not yet been studied in pSS. However, adrenomedullary responses to hypoglycemia were found to be decreased in patients with rheumatoid arthritis and systemic sclerosis suggesting downregulation of the adrenomedullary function in patients with autoimmune diseases.(Rovensky et al. 2008; Imrich et al. 2005; Imrich et al. 2006) The aim of the present study was to evaluate the adrenomedullary hormonal system in patients with pSS.

Subjects and Methods

The study population consisted of a total of 18 patients fulfilling the American-European Consensus Classification criteria for pSS and thirteen (N=13) healthy volunteers serving as a control group. The subjects were studied at the National Institutes of Health Clinical Center after giving informed, written consent to participate in protocols approved by Intramural Review Board of the National Institute of Dental and Craniofacial Research. For each patient, a medical history and physical examination were taken, with emphasis on symptoms and signs of pSS. Drugs known to affect sympathetic neuroeffector function, such as tricyclic antidepressants and sympatholytic agents as well as antihypertensives, were discontinued to allow a five half-lives washout period before the study.

The glucagon test was a part of complex autonomic testing protocol consisting of Valsalva maneuver, tilt table test and edrophonium injection (data not shown). At each visit, the same clinical laboratory tests were performed. Autonomic testing for all subjects was performed between 1:00 PM and 3:00 PM. In all subjects, an antecubital venous catheter was inserted for drawing blood samples and to infuse test drugs. Subjects received 1 mg of glucagon as a bolus intravenous injection. Blood was sampled at baseline and at 1, 2, 3, and 5 minutes after glucagon injection. The glucagon test was performed in a total of 18 pSS patients and 13 control subjects. Beat-to-beat blood pressure was measured non-invasively using a Finometer device (Finapres Medical Systems, Amsterdam, the Netherlands). Each patient also had electrocardiographic and impedance cardiographic monitoring (BioZ, Cardiodynamics, San Diego, CA, USA). Continuous vital signs data were digitized and recorded using a PowerLab (AD Instruments Ltd., Castle Hill, Australia) data acquisition system.

Plasma catecholamines, including norepinephrine, epinephrine, dopamine, dihydroxyphenylalanine, dihydroxyphenylacetic acid and dihydroxyphenylglycol were assayed in the Clinical Neurochemistry Laboratory of the Clinical Neurocardiology Section,

by liquid chromatography with electrochemical detection after batch alumina extraction. (Holmes et al. 1994)

Statistical analyses were performed using IBM SPSS Statistics version 19 (SPSS Inc., Chicago, IL, USA). Changes associated with the glucagon test were analyzed using the General Linear Model for Repeated Measures procedure. Group differences in mean values were analyzed by means of independent means t tests (or the Mann-Whitney u test, depending on normality of the data distributions). Mean values were expressed $\pm$ standard error of mean. A p value less than 0.05 was considered statistically significant.

Results

Basic characteristics of all pSS patients and controls are showed in Table 1. Baseline concentrations of all measured catecholamines were comparable between pSS and controls. Glucagon administration induced a significant increase in systolic blood pressure, diastolic blood pressure, heart rate, cardiac output ($p < 0.01$), stroke volume, systemic vascular resistance transiently decreased ($p < 0.05$) and pre-ejection period shortened ($p < 0.001$). Velocity and acceleration indices also transiently decreased with nadir at 2 min of the glucagon test. pSS patients and controls had comparable responses of blood pressure, heart rate, cardiac output, stroke volume, systemic vascular resistance, velocity and acceleration indices in response to glucagon. Among all catecholamines measured in the study only epinephrine levels increased ($p < 0.01$) in response to glucagon administration (Figure 1). There was no significant difference in neurochemical responses to glucagon between pSS and controls.

Discussion

In the present study we evaluated adrenomedullary function in patients with pSS. Our results show that epinephrine responses to glucagon challenge in pSS patients was comparable with healthy controls suggesting normal adrenomedullary function in pSS. The finding is in contrast to previous observations of lower adrenomedullary response to hypoglycemia in patients with rheumatoid arthritis and systemic sclerosis.

Hypoglycemia and glucagon tests differ in their mechanisms leading to secretion of epinephrine. Whereas epinephrine secretion during hypoglycemia is a part of complex neuroendocrine response triggered in autonomic centers in the hypothalamus, glucagon action is probably restricted to the adrenal medulla or presynaptic nerves innervating the gland. Thus, the glucagon test provides important information on the peripheral gland itself by stimulating adrenomedullary secretion of catecholamines directly. It must be noted that glucagon at the testing dose of 1 mg causes significantly smaller epinephrine response compared to the insulin-induced hypoglycemia test used in earlier studies.(Imrich et al. 2006; Imrich et al. 2005; Rovinsky et al. 2008) Thus, indirect down regulation of adrenomedullary function in pSS might not have been detected in the present study. The precise mechanism of glucagon action in the adrenal medulla is currently unclear. Glucagon receptors were not found to be expressed in normal human adrenal medulla.(Albertin et al. 2001) Nevertheless, the authors of the latter study suggested that the normal human adrenal medulla has a low number of glucagon binding sites and shows a weak catecholamine response to high concentrations of glucagon. The authors also suggested that glucagon may act on receptors for other secretin family peptides, which share amino acid sequence with glucagon and are expressed in the human adrenal medulla.(Albertin et al. 2001; Mazzocchi et al. 2002) An alternative mechanism of glucagon action has been proposed suggesting that plasma epinephrine response to glucagon results from increased sympathetic preganglionic outflow to the adrenal medulla.(Goldstein and Holmes 2008; Sharabi et al. 2005)

One of the strengths of the present study is a novel approach in addressing autonomic dysfunction presence in pSS by evaluating adrenomedullary response to glucagon. Limitations of the study include the relatively small number of subjects and slightly higher BMI in healthy controls compared to pSS patients.

In conclusion, the present results suggest normal adrenomedullary function in pSS.

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References

- Albertin G, Aragona F, Gottardo L, Malendowicz LK, Nussdorfer GG. Human pheochromocytomas, but not adrenal medulla, express glucagon-receptor gene and possess an in vitro secretory response to glucagon. *Peptides*. 2001; 22(4):597–600. [PubMed: 11311729]
- Cox SW, Ebersole LE, Carpenter GH, Proctor GB. Effects of autonomic agonists and immunomodulatory cytokines on polymeric immunoglobulin receptor expression by cultured rat and human salivary and colonic cell lines. *Arch Oral Biol*. 2007; 52(5):411–416. [PubMed: 17118334]
- Dawson LJ, Stanbury J, Venn N, Hasdimir B, Rogers SN, Smith PM. Antimuscarinic antibodies in primary Sjogren's syndrome reversibly inhibit the mechanism of fluid secretion by human submandibular salivary acinar cells. *Arthritis Rheum*. 2006; 54(4):1165–1173. [PubMed: 16572451]
- Elenkov IJ, Kvetnansky R, Hashimoto A, Bakalov VK, Link AA, Zachman K, Crane M, Jezova D, Rovensky J, Dimitrov MA, Gold PW, Bonini S, Fleisher T, Chrousos GP, Wilder RL. Low- versus high-baseline epinephrine output shapes opposite innate cytokine profiles: presence of Lewis- and Fischer-like neurohormonal immune phenotypes in humans? *J Immunol*. 2008; 181(3):1737–1745. [PubMed: 18641310]
- Goldstein DS, Holmes C. Neuronal source of plasma dopamine. *Clin Chem*. 2008; 54(11):1864–1871. [PubMed: 18801936]
- Holmes C, Eisenhofer G, Goldstein DS. Improved assay for plasma dihydroxyphenylacetic acid and other catechols using high-performance liquid chromatography with electrochemical detection. *J Chromatogr B Biomed Appl*. 1994; 653(2):131–138. [PubMed: 8205240]
- Humphreys-Beher MG, Brayer J, Yamachika S, Peck AB, Jonsson R. An alternative perspective to the immune response in autoimmune exocrinopathy: induction of functional quiescence rather than destructive autoaggression. *Scand J Immunol*. 1999; 49(1):7–10. [PubMed: 10023850]
- Imrich R, Lukac J, Rovensky J, Radikova Z, Penesova A, Kvetnansky R, Huckova M, Vigas M, Macho L, Koska J. Lower adrenocortical and adrenomedullary responses to hypoglycemia in premenopausal women with systemic sclerosis. *J Rheumatol*. 2006; 33(11):2235–2241. [PubMed: 17086608]
- Imrich R, Rovensky J, Malis F, Zlnay M, Killinger Z, Kvetnansky R, Huckova M, Vigas M, Macho L, Koska J. Low levels of dehydroepiandrosterone sulphate in plasma, and reduced sympathoadrenal response to hypoglycaemia in premenopausal women with rheumatoid arthritis. *Ann Rheum Dis*. 2005; 64(2):202–206. [PubMed: 15647427]
- Mandl T, Hammar O, Theander E, Wollmer P, Ohlsson B. Autonomic nervous dysfunction development in patients with primary Sjogren's syndrome: a follow-up study. *Rheumatology (Oxford)*. 49(6):1101–1106. [PubMed: 20219783]
- Mandl T, Wollmer P, Manthorpe R, Jacobsson LT. Autonomic and orthostatic dysfunction in primary Sjogren's syndrome. *J Rheumatol*. 2007; 34(9):1869–1874. [PubMed: 17659755]
- Mazzocchi G, Malendowicz LK, Rebuffat P, Gottardo L, Nussdorfer GG. Expression and function of vasoactive intestinal peptide, pituitary adenylate cyclase-activating polypeptide, and their receptors in the human adrenal gland. *J Clin Endocrinol Metab*. 2002; 87(6):2575–2580. [PubMed: 12050216]

- Mori K, Iijima M, Koike H, Hattori N, Tanaka F, Watanabe H, Katsuno M, Fujita A, Aiba I, Ogata A, Saito T, Asakura K, Yoshida M, Hirayama M, Sobue G. The wide spectrum of clinical manifestations in Sjogren's syndrome-associated neuropathy. *Brain*. 2005; 128(Pt 11):2518–2534. [PubMed: 16049042]
- Rovensky J, Imrich R, Penesova A, Radikova Z, Scipova A, Vlcek M, Vigas M. Adrenomedullary response to hypoglycemia in first-degree relatives of patients with rheumatoid arthritis. *Ann N Y Acad Sci*. 2008; 1148:552–555. [PubMed: 19120156]
- Sakakibara R, Hirano S, Asahina M, Sawai S, Nemoto Y, Hiraga A, Uchiyama T, Hattori T. Primary Sjogren's syndrome presenting with generalized autonomic failure. *Eur J Neurol*. 2004; 11(9):635–638. [PubMed: 15379743]
- Sharabi Y, Zimlichman R, Alesci S, Huynh T, Mansouri R, Chun J, Perera S, Pacak K, Goldstein DS. Glucagon does not affect catecholamine release in primary cultures of bovine adrenal chromaffin cells. *Horm Metab Res*. 2005; 37(4):205–208. [PubMed: 15952078]
- Takahashi H, Tsuda Y, Kobayashi M, Herndon DN, Suzuki F. Increased norepinephrine production associated with burn injuries results in CCL2 production and type 2 T cell generation. *Burns*. 2004; 30(4):317–321. [PubMed: 15145188]
- Torres KC, Antonelli LR, Souza AL, Teixeira MM, Dutra WO, Gollob KJ. Norepinephrine, dopamine and dexamethasone modulate discrete leukocyte subpopulations and cytokine profiles from human PBMC. *J Neuroimmunol*. 2005; 166(1–2):144–157. [PubMed: 16026859]
- Wahle M, Greulich T, Baerwald CG, Hantzschel H, Kaufmann A. Influence of catecholamines on cytokine production and expression of adhesion molecules of human neutrophils in vitro. *Immunobiology*. 2005; 210(1):43–52. [PubMed: 16076033]

Figure 1.
Responses of plasma norepinephrine (left) and epinephrine (right) to 1 mg of glucagon i.v. in patients with primary Sjögren's syndrome (pSS) and healthy controls.

Table 1

Basic characteristics of patients with primary Sjögren's syndrome and healthy controls

	pSS	Controls	P value
Number of subjects	18	13	
Gender (M/F)	0 / 18	2 / 11	NS
Age (years)	44.4 ± 3.18	50.77 ± 1.91	NS
Body mass index (kg/m ²)	26.3 ± 1.18	30.67 ± 1.61	0.033
MSG Focus score	3.28 ± 0.61	0.80 ± 0.58	0.055
MSG Atrophy score	0.88 ± 0.21	0.20 ± 0.20	NS

MSG = minor salivary gland

Focus score = number of lymphocytic aggregates (≥ 50 lymphocytes) per 4mm²