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Cell Biology International 32 (2008) 16–21

Cell Biology International

www.elsevier.com/locate/cellbi

IGF-I and INS receptor expression in the salivary glands of diabetic Nod mice submitted to long-term insulin treatment

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Received 28 April 2006; revised 13 July 2007; accepted 17 August 2007

Abstract

This work aimed to characterize the IGF-I and INS receptor expression in the salivary glands of Nod mice, correlating to therapeutic effects of insulin treatment on these receptors. Nod mice were divided into: Groups 1 and 2 (diabetic), Groups 3 and 4 (diabetic with insulin treatment) and Group 5 (non-diabetic). Fragments from the salivary glands were processed for immunohistochemical analysis. The results showed that the prolonged diabetic state led to a steadily increased IGF-I receptor expression. INS receptor expression was gradually decreased. It was concluded that not only was the IGF-I receptor expression affected by the diabetic state but also the INS receptor expression. The period of the diabetic state was directly related to changes in the expression of these receptors. In spite of the insulin treatment having recovered the glycaemic levels, the expression of INS and the IGF-I receptors did not reach the standard level, which certainly hampered glandular function.

Keywords: Salivary glands; Autoimmune diabetes; Insulin treatment; IGF-IR; Insulin receptor

1. Introduction

Various biological processes such as the control of metabolic activities, cellular differentiation, cellular proliferation, apoptotic processes and tumorigenesis are influenced by biologically active peptides including several hormones, such as insulin-like growth factor (IGF) and insulin (INS) (Zumstein and Stiles, 1987; Ryan et al., 1992; Curigliano et al., 2005; Plum et al., 2005; Yakar et al., 2005). All these processes take place in different tissues including salivary glands, the central nervous system and accessory sex glands, among others (Yee et al., 1989; Ryan et al., 1992; Kerr et al., 1995; Schillaci et al., 1998; Djavan et al., 2001; Wetterau et al., 2003; Zhao et al., 2004; Bahr and Groner, 2005; Marszalek et al., 2005).

Insulin is found in blood plasma after being secreted by beta cells from the pancreas, stimulated by the blood glucose level (Nattras and Halles, 1988). Insulin-like growth factors, including IGF-I and IGF-II, are found in blood plasma and different cellular types from mammals can synthesise and export them. The IGF regulatory system in each organ is tissue-specific (Djavan et al., 2001).

In the salivary glands, insulin-like growth factors are synthesized in the acinar cells, especially in the region of the secretary ducts, not only in the human species but also in rodents (Smith and Patel, 1984; Hansson and Tunhall, 1988; Ryan et al., 1992; Humphreys-Beher et al., 1994). IGF and insulin effects are mediated by specific membrane receptors. There are two membrane IGF receptors, which resemble the insulin receptor. Thus, IGF-I, IGF-II and insulin can all blind to the IGF-I receptor with a ratio affinity of 100:10:1, respectively (Jones and Clemmons, 1995).

Diabetes mellitus is a metabolic disorder in which the functional mechanisms of both insulin and IGF are changed (Kerr et al., 1995). Studies showed that chemically induced diabetes in both rats and mice led to diminished insulin levels in the acinar cells of the parotid and submandibular glands after periods which varied from 7 to 27 days (Smith and Patel, 1984; Patel et al., 1986). Also, Kerr et al. (1995) observed

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doi:10.1016/j.cellbi.2007.08.005

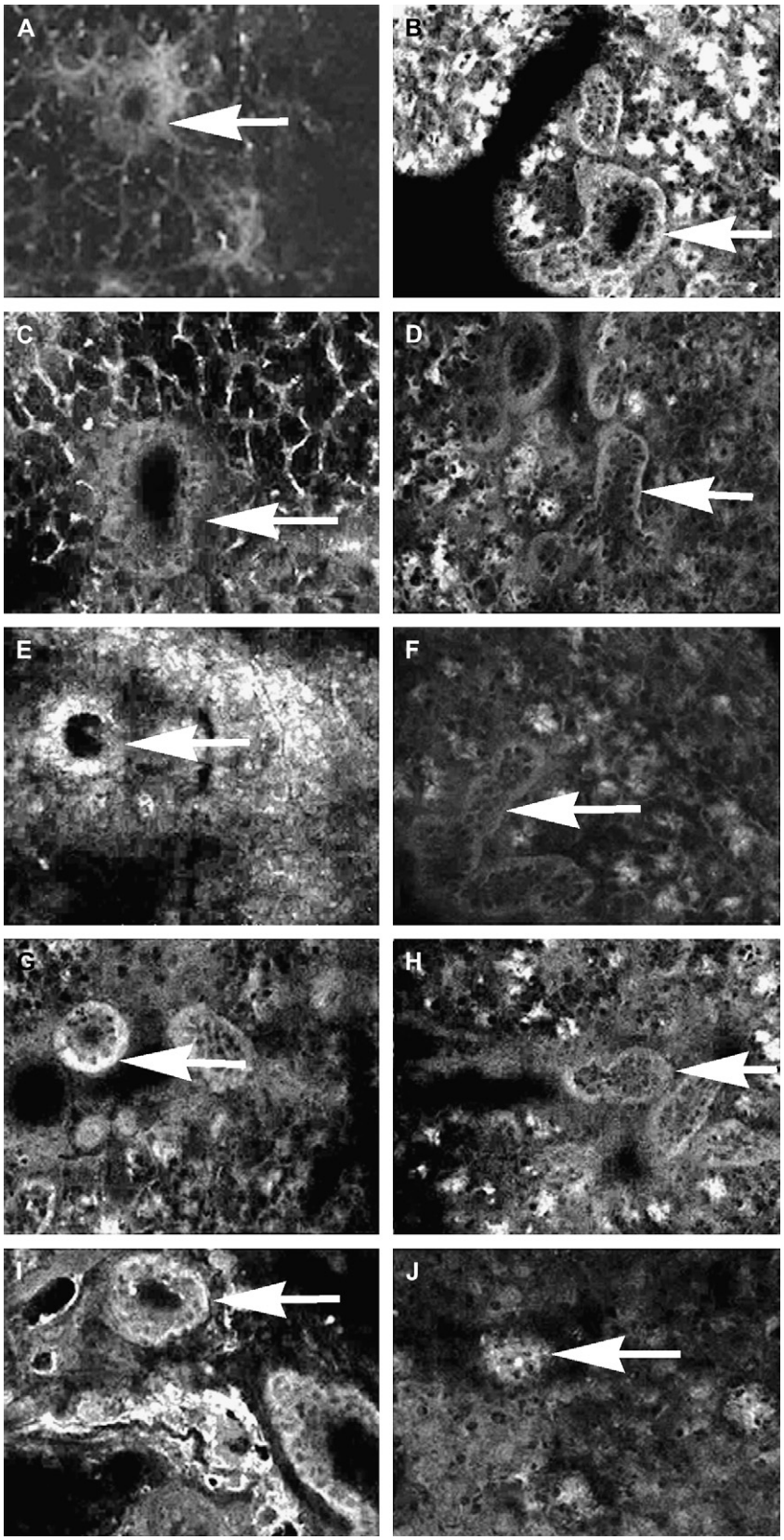

Fig. 1. Immunolocalization of the insulin and IGF-I receptors on the parotid glands. (A) Non-diabetic mice (Group 5); secretory ducts cells showing moderate IGF-I receptor expression (arrow). (B) Non-diabetic mice (Group 5); intense insulin receptor expression, placed, especially in the glandular duct cells (arrow). (C) Diabetic mice for 10 days (Group 1); secretory duct cells presenting intense IGF-I receptor expression (arrow). (D) Diabetic mice for 10 days (Group 1); glandular duct cells with moderate insulin receptor expression (arrow). (E) Diabetic mice for 20 days (Group 2); glandular duct cells showing intense IGF-I receptor expression (arrow). (F) Diabetic mice for 20 days (Group 2); secretory duct cells showing weak insulin receptor expression (arrow). (G) Diabetic mice for 10 days with insulin treatment (Group 3); intense IGF-I receptor expression (arrow). (H) Diabetic mice for 10 days with insulin treatment (Group 3); moderate insulin receptor expression (arrow). (I) Diabetic mice for 20 days with insulin treatment (Group 4); secretory duct cells presenting intense IGF-I receptor expression (arrow). (J) Diabetic mice for 20 days with insulin treatment (Group 4); weak insulin receptor expression (arrow). Magnification: 400×.