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Hyperalgesia in non-obese diabetic (NOD) mice: A role for the inducible bradykinin B_1 receptor

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Abstract

Most studies performed to investigate the role of the inducible bradykinin B_1 receptor in the pathology and complications of type 1 diabetes have been carried out using the model of streptozotocin (STZ)-induced diabetes. The model of spontaneous autoimmune diabetes in non-obese diabetic (NOD) mice involves a long-term inflammatory process that closely resembles the human type 1 diabetes.

In the present study, we aimed at establishing the correlation between the progress of diabetic hyperalgesia and the incidence of diabetes, as a function of age, in NOD mice. We also evaluated the implication of the bradykinin B_1 receptor, a receptor up-regulated during the inflammatory progress of diabetes, in the development of diabetic hyperalgesia in NOD mice. Female NOD mice were followed up from the 4th to the 32nd week of age for the incidence of diabetes. Only NOD mice with plasma glucose concentration >20 mmol/l were considered diabetic. The nociception was assessed using the hot plate and the tail immersion pain tests and the effect of acute and chronic administration of the selective bradykinin B_1 receptor agonist, desArg^{9}bradykinin and its selective antagonists, R-715 (Ac-Lys-[D-β Nal^7, Ile^8]desArg^{9}bradykinin) and R-954 (Ac-Orn-[Oic^2, α-MePhe^5, D-β Nal^7, Ile^8]desArg^{9}bradykinin), on the development of diabetic hyperalgesia was studied.

Diabetic NOD mice developed a significant time-dependent hyperalgesia, as measured in both tests, starting from the 8th week of age with the maximum effect observed over 16 to 20 weeks, whereas the incidence of diabetes in the tested NOD mice was only 40.16% at the age of 16 weeks and reached a maximum of 73.23% at the age 24 weeks. Both acute and chronic administration of desArg^{9}bradykinin (400 μg/kg) markedly increased the hyperalgesic activity in diabetic NOD mice in the hot plate and tail immersion nociceptive tests. The selective bradykinin B_1 receptor antagonist R-715 (400 μg/kg) and its more potent and long acting analogue R-954 (200 μg/kg), administered in acute or chronic manner, significantly attenuated diabetic hyperalgesia in NOD mice in both thermal pain tests and restored nociceptive responses to values observed in control non-diabetic siblings.

Our results bring the first evidence that the development of hyperalgesia in NOD mice, a model of spontaneous type 1 diabetes, precedes the occurrence of hyperglycemia and is mediated by the bradykinin B_1 receptor. It is suggested that bradykinin B_1 receptor antagonism could become a novel therapeutic approach to the treatment of diabetic neuropathic complications.

Keywords: Type 1 diabetes; Non-obese diabetic mice; Hyperalgesia; Kinin; Bradykinin B_1 receptor; desArg^{9}bradykinin; R-715; R-954

1. Introduction

Autoimmune type 1 diabetes is the result of a breakdown of self-tolerance. It is associated with an over-production of cytokines, including interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), which leads to T-cell-mediated pancreatic β-cell destruction (Hussain et al., 1996; Rabinovitch and Suarez-Pinzon, 1998; Rabinovitch, 1998). These initial events are associated with an inflammatory reaction and the release of an array of mediators including kinins.

Kinins are key mediators implicated in a variety of biological effects such as cardiovascular homeostasis, inflammation and nociception (Regoli and Barabé, 1980). The bradykinin B_1 receptor, generally silent or absent in

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healthy states, is induced or activated under pathological conditions including type 1 diabetes, where the over-production of cytokines, the hyperglycemia and the oxidative stress are critical factors for its up-regulation (Marceau et al., 1998; Couture et al., 2001).

Most studies performed to investigate the role of the inducible bradykinin B_1 receptor in the pathology and complications of type 1 diabetes have been carried out using animal models of streptozotocin (STZ)-induced diabetes. Accumulating evidence shows the up-regulation of the bradykinin B_1 receptor subtype in STZ-diabetic animal models. It has been reported that the bradykinin B_1 receptor is over-expressed in the stomach of STZ-diabetic mice since the sensitivity of the stomach fundus to desArg^{9}bradykinin was substantially increased in these animals compared to control non-diabetic mice (Pheng et al., 1997). Lung macrophages and fibroblasts from STZ-diabetic rats express the bradykinin B_1 receptor and their activation leads to the release of cytokines (Koyama et al., 2000). In addition, the bradykinin B_1 receptor is induced at the peripheral terminals of C-fibers and on the endothelial cells in the lung of STZ-diabetic rats and its activation was shown to be associated with the release of substance P (Vianna et al., 2003). The bradykinin B_1 receptor subtype is also expressed in the kidney and spinal cord of STZ-treated mice (Cloutier and Couture 2000; Mage et al., 2002).

A crucial role has been attributed to the bradykinin B_1 receptor subtype in the development of hyperglycemia and renal abnormalities (Zucollo et al., 1996, 1999; Cantazaro et al., 2004) as well as in altered vascular permeability (Simard et al., 2002) in STZ-induced diabetic animals. Also, we recently demonstrated that STZ-induced diabetes is associated with a marked hyperalgesia in mice, developing 1 week following STZ injection. Such hyperalgesic activity is significantly reduced by both the acute or chronic administration of selective bradykinin B_1 receptor antagonists (Gabra and Sirois, 2002, 2003a,b).

The model of spontaneous autoimmune diabetes in non-obese diabetic (NOD) mice involves a long-term inflammatory process that closely resembles the human type 1 diabetes (Tisch and McDevitt, 1996). It results from a $CD4^+$ and $CD8^+$ T cell-dependent autoimmune process directed against the pancreatic β-cells (Serreze and Leiter, 1994; Tisch and McDevitt, 1996). The major histocompatibility complex (MHC) of the NOD mice (designated $H2^{g7}$) contributes the main component of susceptibility (similar to humans). The MHC class II I-Aβ chain shows the same diabetogenic amino acid substitution (at residue 57) associated with a high risk of development of type 1 diabetes in humans (Atkinson and Leiter, 1999). Non-obese diabetic mice develop inflammation of pancreatic islets (insulitis) at 3 weeks of age, but do not begin to develop diabetes until 10 weeks later (Delovitch and Singh, 1997). There is sexual dimorphism in the incidence of diabetes in NOD mice in most of the colonies. The disease occurs earlier and more often in females, with an incidence reaching up to 70%, compared to males in which the overall incidence remains below 20% (Fitzpatrick et al., 1991).

The present study aimed at evaluating the development of hyperalgesia in female NOD mice and characterizing the role of the inducible bradykinin B_1 receptor subtype, up-regulated during the inflammatory progress of diabetes, in such a complication.

2. Materials and methods

2.1. Animals

Female NOD/LtJ mice (Taconic Farms, Inc., Germantown, NY, USA) and female age-matched CD-1 mice (Charles River Breeding Laboratory, St-Constant, PQ, Canada) were used. The mice were housed four by cage with free access to food and water. They were maintained under conditions of standard lighting, (alternating 12-h light/dark cycle), temperature (22 ± 0.5 °C) and humidity (60 ± 10%) with food and water available ad libitum. Animals were used only once in a given experiment. All experiments were carried out in accordance with the recommendations of the IASP (International Association for the Study of Pain) Committee for Research and Ethical Issues Guidelines and were approved by the Animal Care Committee of the University of Sherbrooke.

2.2. Follow-up of diabetes incidence in NOD mice

Mice were screened twice weekly, from 4 to 32 weeks of age, for diabetes onset by measuring urine and plasma glucose concentrations. Urine glucose concentration was determined using reagent strips for urinalysis (Uristix, Bayer Diagnostics, Toronto, ON, Canada). Blood was withdrawn from the retro-orbital sinus of mice with a 50-μl heparinized capillary tube. Plasma glucose concentration was determined with an automatic analyzer (Glucometer Elite XL, Bayer Incorporation, Toronto, ON, Canada) using glucose oxidase/potassium ferricyanide reagents strips. Mice were considered to be diabetic after two consecutive urine glucose concentrations >5.5 mmol/l and a plasma glucose concentration ≥20 mmol/l.

2.3. The hot plate test

A hot plate test (supraspinal pain) derived from that of Eddy and Leimbach (Eddy and Leimbach, 1953) was used. The mouse was placed on a IITC Hot Plate Analgesia Meter (Life Science, CA, USA) adjusted at 55 ± 0.5 °C. The hot plate response was the latency observed from the time the mouse was placed on the heated surface until the first overt behavioural sign of nociception such as (i) the mouse licking a hind paw, (ii) vocalization, or (iii) an escape

response. The timer was stopped by a foot-operated pedal and the mouse immediately removed from the hot plate. Only mice with basal latency value between 10 and 15 s were selected and a maximum cut-off time of 30 s was observed to avoid excessive pain.

2.4. The tail immersion test

The tail immersion (spinal pain) test was performed according to Coderre and Rollman (1983). The mouse is gently wrapped in a towel, held at a 45° angle to a thermostatically controlled water bath set at 52±1 °C. The latency between submersion of the tail and its removal from the water by the animal is recorded, with a maximum cut-off time of 10 s to avoid excessive pain. Mice with latency value between 2.5 and 4.0 s were selected.

2.5. Drugs

desArg^{9}bradykinin, R-715 (Ac-Lys-[D-β Nal^7, Ile^8]desArg^{9}bradykinin) (Regoli et al., 2001) and R-954 (Ac-Orn-[Oic^2, α-MePhe^5, D-β Nal^7, Ile^8]desArg^{9}bradykinin) (Neugebauer et al., 2002) were supplied by IPS Pharma Inc. (Sherbrooke, PQ, Canada).

2.6. Experimental protocol

In a first series of experiments, the development of hyperalgesia in NOD mice was studied. Nociception was assessed once weekly, from 4 to 32 weeks of age using the hot plate and the tail immersion tests.

In a second series of experiments, the effect of acute administration of the selective bradykinin B_1 receptor agonist, desArg^{9}bradykinin (400 μg/kg) and its specific antagonists R-715 (400 μg/kg) and R-954 (200 μg/kg) on diabetic hyperalgesia in NOD mice was evaluated. The peptides were administered intraperitoneally (i.p.) to diabetic NOD mice at the age of 24–32 weeks (when the hyperalgesia was maximal and stable). The hot plate and tail immersion latencies were measured, 20 min later.

A final series of experiments was done to study the chronic effects of desArg^{9}bradykinin (400 μg/kg), R-715 (400 μg/kg) and R-954 (200 μg/kg) in diabetic NOD mice. At the age of maximal hyperalgesia, NOD mice were given desArg^{9}bradykinin, R-715 or R-954 i.p., twice daily, for 7 days. By the end of this chronic treatment, the effect of bradykinin B_1 receptor-related peptides was evaluated on nociception using the same thermal pain tests, 5 h following the last dose of the agonist or the antagonist.

NOD mice siblings, which did not become diabetic, were used as control. The selected doses for desArg^{9}bradykinin and R-715 were found to produce maximal effects as previously published (Gabra and Sirois, 2002, 2003a,b). The hot plate and tail immersion responses are presented as percent of basal latency.

2.7. Statistical analysis

Data are expressed as mean values±S.E.M. Analysis of variance (ANOVA) followed by the "Student–Newman–Keuls Multiple Comparisons Test" were performed to assess significance using the Instat 3.0 software (GraphPad Software, San Diego, CA, U.S.A.). $P<0.05$ was considered significant.

3. Results

3.1. Plasma glucose concentration

As illustrated in Fig. 1, female diabetic NOD mice showed a marked age-dependent increase in their plasma glucose concentration compared to control non-diabetic siblings. The first significant rise in the plasma glucose concentration was observed in diabetic NOD mice at 11–12 weeks of age and reached 19.58±2.02 mmol/l compared to 5.08±0.45 mmol/l in non-diabetic siblings. The plasma glucose concentration continued to increase with age until it reached a plateau over 24–32 weeks of age (≅35 mmol/l).

3.2. Diabetes incidence

The profile of diabetes incidence in diabetic female NOD mice, as a function of age, is shown in Fig. 2. Female NOD mice had an incidence of 5.52% (7 out of 127 mice) at the age of 12 weeks, but none showed evidence of diabetes before this age as evaluated by glucose concentrations in urine and plasma. They reached an incidence of 40.16% (51

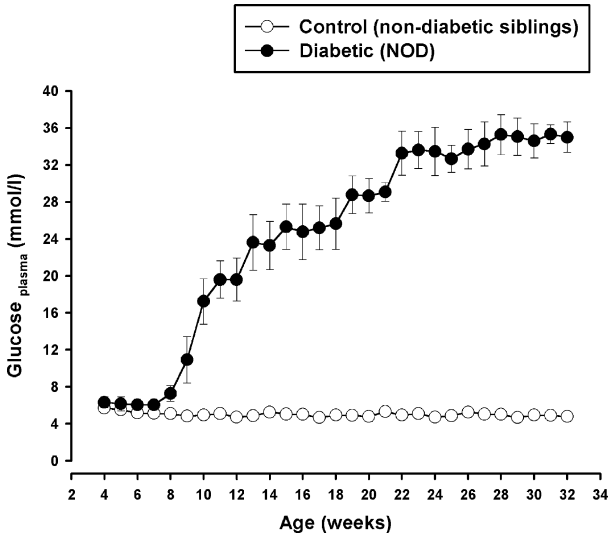

Fig. 1. Plasma glucose concentration in diabetic NOD mice and control non-diabetic siblings. Mice were screened twice weekly, from 4 to 32 weeks of age, for their plasma glucose concentration using an automatic analyzer and were considered diabetic after a plasma glucose concentration ≥20 mmol/l. $n=93$ diabetic and 34 non-diabetic. Data are expressed as mean plasma glucose concentration±S.E.M.

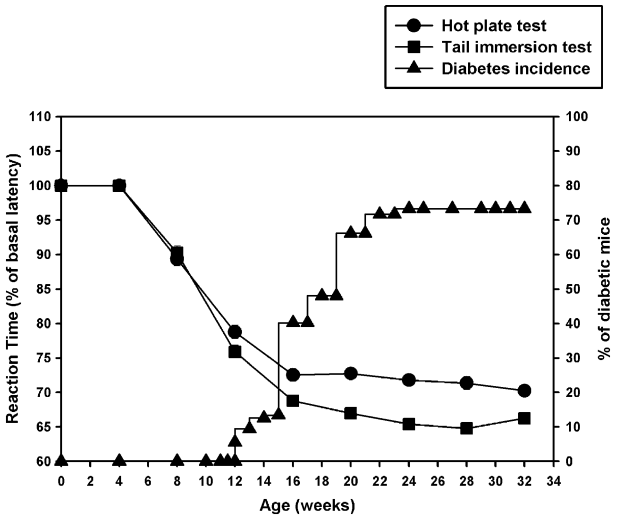

Fig. 2. Correlation between the development of hyperalgesia and the onset of diabetes in female diabetic NOD mice. Nociception was assessed once weekly, from 4 to 32 weeks of age using the hot plate and the tail immersion tests. Mice were screened twice weekly for diabetes onset over the same age period by measuring urine and plasma glucose concentrations ($n=93$). The hot plate ($n=48$) and the tail immersion ($n=45$) latencies are expressed as mean percent of basal latency ± S.E.M.

out of 127 mice) at the 16th week of age, whereas a maximum incidence of 73.23% (93 out of 127 mice) was observed at 24 weeks of age.

3.3. Correlation between hyperalgesia and diabetes onset

The results showed that diabetic NOD mice develop a significant time-dependent hyperalgesia starting from the 8th week of age with the maximum effect observed over 16 to 20 weeks (Fig. 2). At the age of 8 weeks, the percent of the hot plate basal latency in diabetic NOD mice was 89.37 ± 1.04 versus 99.78 ± 0.29% in control non-diabetic siblings and the hyperalgesic effect reached its maximum by the 16th week of age when the percent of the hot plate basal latency was 72.52 ± 0.78% in diabetic NOD mice compared to 98.97 ± 0.18% in control non-diabetic siblings ($n=48$; $P<0.001$). Similarly, at the age of 8 weeks, the percent of the tail immersion basal latency was significantly decreased (90.22 ± 1.00%) in diabetic NOD mice compared to non-diabetic siblings (99.75 ± 1.06%). The maximum hyperalgesic effect was observed at 20 weeks of age, when the percent of the tail immersion basal latency in diabetic NOD mice was 66.98 ± 0.54% compared to 96.87 ± 1.23% in control non-diabetic siblings ($n=45$; $P<0.001$). The hyperalgesic activity reached a plateau from the 16th to the 32nd week of age in the hot plate test and from the 20th to the 32nd week in the tail immersion test.

It is noteworthy that NOD mice siblings, which did not become diabetic, showed no changes in their response to thermal nociceptive tests over the period from 4 to 32 weeks of age (Fig. 3A and B).

3.4. Effects of acute administration of desArg^{9}bradykinin, R-715 and R-954 to NOD mice

The exogenous administration of the selective bradykinin B_1 receptor agonist, desArg^{9}bradykinin (400 μg/kg, i.p.) at the age of maximal hyperalgesia (24–32 weeks), markedly increased the hyperalgesic activity observed in diabetic NOD mice in the hot plate (Fig. 3A) and the tail immersion

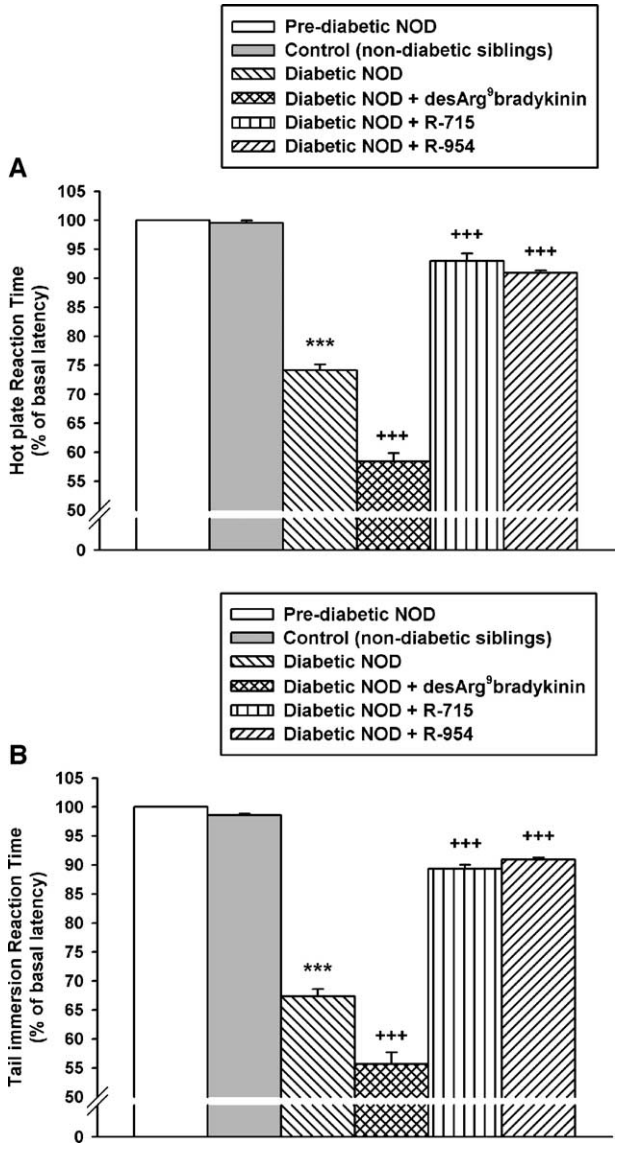

Fig. 3. Effects of acute administration of the selective bradykinin B_1 receptor agonist, desArg^{9}bradykinin and its selective antagonists, R-715 and R-954 on hyperalgesia in female NOD mice. Nociception was assessed in pre-diabetic (4 weeks of age), control (non-diabetic siblings) and diabetic NOD mice using the hot plate (A) and the tail immersion (B) tests. desAr^{9}bradykinin (400 μg/kg), R-715 (400 μg/kg) and R-954 (200 μg/kg) were given to mice by i.p. injection. The hot plate and the tail immersion latencies were measured 20 min post-treatment. For each animal, data are expressed as mean percent of basal latency ± S.E.M. ($n=8–10$). ***Values significantly different from control non-diabetic siblings at $P<0.001$ and $^{+++}$values significantly different from diabetic NOD mice at $P<0.001$.

(Fig. 3B) tests. The percent of the hot plate and tail immersion latency compared to the basal latency in desArg^{9}bradykinin-treated diabetic NOD mice was 58.38±1.48 and 55.71±1.95%, respectively, versus 74.13±0.99 and 67.33±1.23% in untreated diabetic NOD mice (n=8–10; P<0.001).

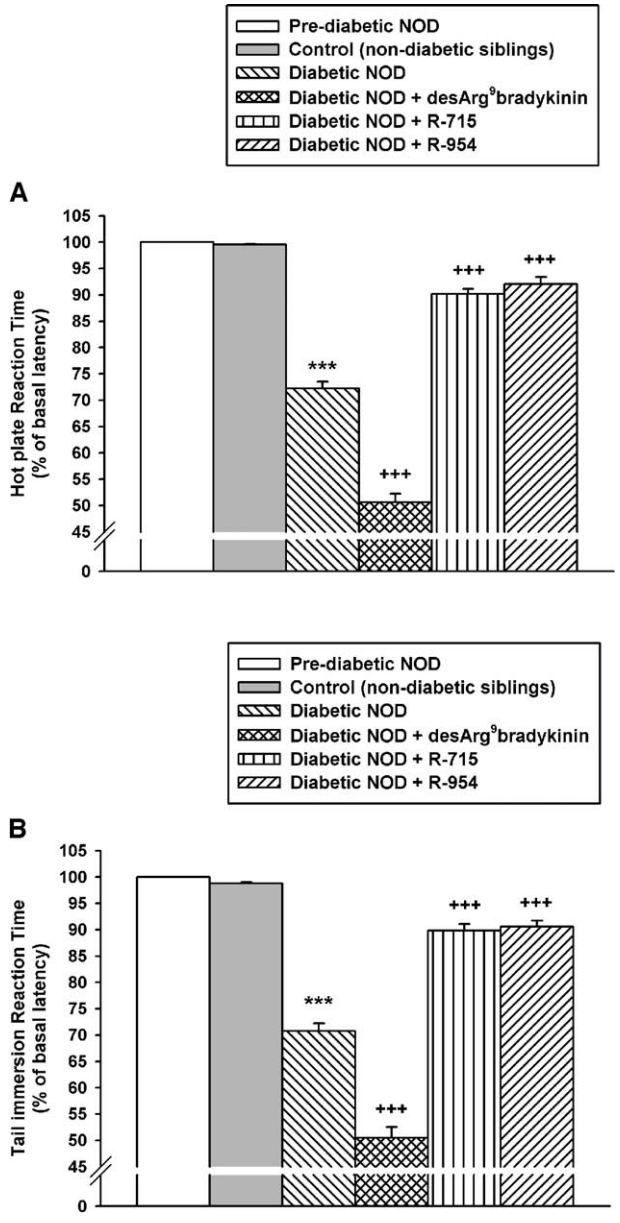

Fig. 4. Effects of chronic administration of the selective bradykinin B_1 receptor agonist, desArg^{9}bradykinin and its selective antagonists, R-715 and R-954 on hyperalgesia in female NOD mice. Nociception was assessed in pre-diabetic (4 weeks of age), control (non-diabetic siblings) and diabetic NOD mice using the hot plate (A) and the tail immersion (B) tests. desArg^{9}bradykinin (400 μg/kg), R-715 (400 μg/kg) and R-954 (200 μg/kg) were administered (twice daily for 7 days) to mice by i.p. injection. The hot plate and the tail immersion latencies were measured 5 h following the last treatment. For each animal, data are expressed as mean percent of basal latency±S.E.M. (n=8–9). ***Values significantly different from control non-diabetic siblings at P<0.001 and $^{+++}$values significantly different from diabetic NOD mice at P<0.001.

Acute administration of the selective bradykinin B_1 receptor antagonists R-715 and R-954 to diabetic NOD mice abolished hyperalgesia and restored nociceptive responses to values observed in control non-diabetic siblings (Fig. 3A and B). R-715 (400 μg/kg, i.p.) restored the percent of basal latency to 92.99±1.29 and 89.34±0.73% and R-954 (200 μg/kg, i.p.) to 90.93±0.43 and 90.91±0.39% in the hot plate and the tail immersion tests, respectively (n=8–9; P<0.001).

It is worth mentioning that desArg^{9}bradykinin, R-715 and R-954, tested in control non-diabetic siblings, had no effect at all on the hot plate and tail immersion reaction times (data not shown).

3.5. Effects of chronic administration of desArg^{9}bradykinin, R-715 and R-954 to NOD mice

The chronic administration of desArg^{9}bradykinin, R-715 and R-954 to NOD mice gave similar effects than the acute administration. In brief, the twice daily injection of desArg^{9}bradykinin for 7 days, starting at the age of maximal hyperalgesia (24-32 weeks), increased, whereas that of R-715 and R-954 decreased, hyperalgesia in diabetic NOD mice (Fig. 4A and B). The bradykinin B_1 receptor agonist, desArg^{9}bradykinin reduced the percent of the hot plate and tail immersion latency compared to the basal latency to 50.61±1.64% and 50.51±2.03%, respectively, versus 72.23±1.29 and 70.77±1.46% in untreated diabetic NOD mice (n=8–9; P<0.001).

The selective bradykinin B_1 receptor agonist, R-715 significantly increased the percent of hot plate latency to 90.20±0.92% and the percent of tail immersion latency 89.86±1.23%, whereas the more potent analogue R-954 increased the hot plate and tail immersion percent latency to 95.04±1.34 and 90.55±1.17%, respectively (n=8–9; P<0.001).

4. Discussion

In the present study, we showed for the first time the development of a time-dependent hyperalgesia in NOD mice, a model of spontaneous autoimmune type 1 diabetes. We also demonstrated that the observed hyperalgesia does not correlate with the increase in the plasma glucose concentration of the NOD mice, but rather appears very early alongside diabetes and is significant at young age (8–10 weeks), preceding the hyperglycaemic state of the mice. These results are in agreement with our previous findings which showed that STZ-induced diabetes in CD-1 mice is associated with a marked hyperalgesia in thermal nociceptive tests (Gabra and Sirois, 2002, 2003a,b) and suggest that diabetic complications, including hyperalgesia, start to develop during the early inflammatory stages of the disease, even before establishing the hyperglycemia and/or the glucosuria-based diagnosis for diabetes. This could be due

to the over-production of cytokines and the oxidative stress developing during the autoimmune response in diabetes as well as the subsequent activation of the mitogen-activated protein kinase (MAP-kinase) and the transcriptional nuclear factor κB (NF-κB) pathways (Couture et al., 2001).

Our results confirm the involvement of the inducible bradykinin B_1 receptor subtype in mediating hyperalgesia observed in murine models of type 1 diabetes. Both acute and chronic administration of the selective bradykinin B_1 receptor agonist, desArg^{9}bradykinin significantly increased the hyperalgesic effect in diabetic NOD mice, whereas the selective bradykinin B_1 receptor antagonists, R-715 and R-954 were able to abolish such hyperalgesia.

The results obtained also support the previous findings on the expression profile of the bradykinin B_1 receptor in other animal models of type 1 diabetes and the involvement of this receptor subtype in diabetic complications (Koyama et al., 2000; Simard et al., 2002; Mage et al., 2002; Vianna et al., 2003; Cantazaro et al., 2004). The bradykinin B_1 receptor was recently shown to be up-regulated early in the retina of STZ-diabetic rats, 4 days and up to 21 days, following STZ injection (Abdouh et al., 2003). In the same study, selective bradykinin B_1 receptor agonists evoked relaxation of the retinal vessels and the levels of bradykinin B_1 receptor binding sites remained steady and high over 21 days. Moreover, other studies coming from the same laboratory showed a significant increase in the level of the bradykinin B_1 receptor mRNA expression in the spinal cord and brain of STZ-diabetic rats (2 and 7 days following the injection of STZ) and of its specific binding sites (2, 7 and 21 days following STZ injection) (Ongali et al., 2004). Nevertheless, studies are ongoing in our laboratory to evaluate the profile of expression of the bradykinin B_1 receptor in NOD mice in selected tissues including the spinal cord. Preliminary results obtained show the induction of the bradykinin B_1 receptor in the kidney and the vasculature of the spinal cord of diabetic NOD mice starting from 6 to 32 weeks of age (data not shown).

The present results are also consistent with those provided by Pesquero et al., (2000) who demonstrated that in bradykinin B_1 receptor-knockout mice, tissue reactions to microbial toxins, local inflammatory agents, and painful thermal and inflammatory stimulations are reduced without any apparent physiological or behavioural impairments. We have also proved that the hyperalgesic activity clearly manifested in type 1 diabetic wild type C57BL/6 mice, is absent in STZ-diabetic bradykinin B_1 receptor-knockout genotype in which desArg^{9}bradykinin has no effect on nociceptive responses (Gabra et al., 2005).

The hyperalgesic effect observed in diabetic NOD mice, its potentiation by the selective bradykinin B_1 receptor agonist desArg^{9}bradykinin, as well as the antihyperalgesic effect of the selective bradykinin B_1 receptor antagonists, R-715 and R-954, strongly support a role for the bradykinin B_1 receptor in diabetic neuropathy. The bradykinin B_1 receptor subtype, selectively activated by bradykinin B_1 receptor agonists, is absent or of little impact under normal physiological conditions (Couture et al., 2001), but over-expressed in pathological conditions such as diabetes. The up-regulation of the bradykinin B_1 receptor in type 1 diabetes is attributed to several mechanisms including the cytokines (IL-1β and TNF-α)-induced activation of the MAP-kinase and NF-κB pathways (Larrivée et al., 1998; Ni et al., 1998; Schanstra et al., 1998; Zhou et al., 1998; Sardi et al., 1998; Campos et al. 1999). In addition, hyperglycemia and the resulting oxidative stress observed alongside diabetes can activate NF-κB (Yerneni et al., 1999), which is known to induce the bradykinin B_1 receptor (Marceau et al., 1998). Therefore, both the over-production of cytokines and hyperglycemia could trigger the expression of the bradykinin B_1 receptor through NF-κB in diabetes. Moreover, the long-term exposure of the bradykinin B_1 receptor to its endogenous agonist desArg^{9}bradykinin results in increased receptor expression (Faussner et al., 1999). Finally, the bradykinin B_1 receptor was shown to be cross up-regulated by the bradykinin B_2 receptor activation (via autocrine production of cytokines and activation of NF-κB) and/or bradykinin B_2 receptor sensitization (Phagoo et al., 1999).

Chronic activation of the inducible bradykinin B_1 receptor in diabetes is likely to be amplified by the accumulation of desArg^{9}bradykinin and other metabolites resulting from the degradation of kinins at the site of inflammation. Thus, desArg^9 metabolites may directly induce hyperalgesia by stimulating the inducible bradykinin B_1 receptor on sensory neurones to release substance P, calcitonin gene-related peptide, neurokinin A and other nociceptive neurotransmitters (Couture et al., 2001) or by activation of the bradykinin B_1 receptor induced on selected cell types (macrophages, fibroblasts or endothelial cells) with the subsequent release of mediators (prostaglandins, cytokines and nitric oxide) that sensitize the nociceptors (Dray and Perkins, 1997).

In conclusion, the bradykinin B_1 receptor subtype appears to play a major role in mediating hyperalgesia in type 1 diabetic mice. Thus, this receptor emerges as a new target of great potential for the development of specific and selective antagonists directed to reduce the generally excessive responses that are used by the body to counteract noxious stimuli in diabetic patients.

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