Nitrendipine Improves Glucose Tolerance and Deoxyglucose Uptake in Hypertensive Rats

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Abstract  We assessed the effect of the vasodilating calcium channel blocker nitrendipine on glucose tolerance in young spontaneously hypertensive rats (SHR) (n=15). The nitrendipine group received 1 g/kg chow for 3 weeks. Untreated SHR (n=14) served as controls. At 3 weeks body weight was comparable, whereas systolic blood pressure was 157±9 mm Hg in nitrendipine-treated rats versus 191±10 mm Hg in controls (mean±SD, P<.00001). Fasting glucose was 6.8±2.7 mmol/L in nitrendipine-treated versus 8.9±1.5 mmol/L in control rats (P<.03). An intravenous glucose tolerance test (300 mg/kg) showed plasma glucose levels at 2, 5, 15, and 30 minutes to be significantly lower in the nitrendipine-treated group versus controls (two-way ANOVA, P<.03). Glucose utilization was estimated by the uptake of [3H]deoxyglucose after its intravenous administration (2 μCi/100 g body wt) to instrumented awake animals. Heart and striated muscle uptake was, respectively, 7983±5812 and 951±731 cpm/μL · g · min in the nitrendipine-treated group versus 3532±2316 and 424±201 cpm/μL · g · min in controls (P<.02 and P<.04, respectively). [3H]Deoxyglucose plasma half-life and fasting and post-glucose load insulin levels were comparable in the two groups. The results show that nitrendipine improves glucose tolerance by increasing muscle glucose uptake. We suggest that glucose tolerance in SHR is influenced by muscle blood flow and can be improved by vasodilation. (Hypertension. 1994;23[part 2]:1051-1053.)

Key Words • hypertension, genetic • glucose • insulin resistance • nitrendipine • deoxyglucose

Methods

SHR weighing approximately 150 g were obtained from the animal farm of the Tel Aviv University. They were housed in regular cages and maintained on a 12-hour light/dark cycle. They were fed grain regular chow (Kofflok) and had free access to tap water. The chow contained 56% grain-derived carbohydrate, 20% protein, 13% moisture, 5.5% cellulose, 3% fat, 0.8% calcium, 0.6% phosphorus, and 0.3% NaCl. Rats were weighed at weekly intervals, and their systolic BP was measured (prewarmed) by the tail-cuff method using a USM 105 BP recorder (Ueda Electronic Works). All animal housing and handling were in accordance with the guidelines and manual of the Committee on the Care of Laboratory Animals of the Hebrew University Hadassah School of Medicine.

After a week of habituation rats were divided into two groups: a control group (n=14) (weight, 166±26 g) and a nitrendipine-treated group (n=15) (weight, 171±26 g). The drug was mixed daily with ground food (1 g/kg chow) and kept in a light-protected trough. After 3 weeks of treatment rats were anesthetized with ether, and PE-50 canulas were inserted into the femoral artery and vein and exteriorized subcutaneously at the interscapular area. Canulas were filled with heparinized saline solution (100 μU/mL). Forty-eight hours later awake control rats were injected through the femoral vein catheter with a tracer dose of [3H]DG (2 μCi/100 g body wt). Simultaneously, the rats were given a bolus injection of a glucose solution (50%, 300 mg/kg) for assessment of glucose tolerance. Arterial blood was collected from the femoral artery catheter for measurement of [3H]DG and glucose plasma levels.

Rats were decapitated 30 minutes after the injection, and blood was collected for measurement of glucose, [3H]DG, and insulin. Samples of spleen, heart, and striated muscle (gastrocnemius) were frozen in liquid nitrogen and used for tissue [3H]DG determinations.17,18,20 Uptake of [3H]DG by rat tissues was determined as originally described by Sokoloff et al,17 Hom et al,18 and us,19,20 with the modification that tissue uptake was related to the area under the [3H]DG curves.

Glucose was determined by the glucose dehydrogenase assay (glucose GDH, Hoffman–La Roche) and insulin with the WS-RIA 100 radioimmunoassay kit (Medgenix).

Values are expressed as mean±SD except in figures where mean±SEM is shown. Glucose disappearance rate (percent
Results

Both nitrendipine and control SHR gained weight similarly throughout the experiment. As shown in Fig 1, nitrendipine prevented the increase in BP that occurred in control SHR \(F(1,18)=57.17, P=.00001\); pairwise comparison showed that, at least during the final 2 weeks, BP was persistently lowered by nitrendipine \(P<.00001\).

Baseline glucose was significantly lower in nitrendipine SHR (6.8±2.7 mmol/L) than controls (8.9±1.5 mmol/L, \(P<.03\)). The results of the intravenous glucose tolerance test (Fig 2) show that nitrendipine SHR had lower plasma glucose levels throughout the test \(F(1,25)=5.34, P<.03\). The glucose disappearance rate was higher (1.7±0.007 %/min) in nitrendipine than control SHR (1.1±0.008 %/min, \(P<.05\)). Baseline and postload insulin levels were not different between nitrendipine and controls. The respective values for nitrendipine and controls at time 0 were 245±120 (40.8±20.0 \(\mu\)U/mL) and 247±95 pmol/L (41.1±15.8 \(\mu\)U/mL) and, at 30 minutes, 276±156 (46±26 \(\mu\)U/mL) and 247±126 pmol/L (41±21 \(\mu\)U/mL). Fig 3 displays the plasma \([\text{H}]\text{DOG}\) curves. The area under these curves was 453±186 cpm·min·\(\mu\)L in controls and 464±139 cpm·min·\(\mu\)L in nitrendipine SHR. Two-way ANOVA did not indicate any difference between the two groups \(F(1,22)=0.23, P=.611\). Thus, the significantly higher \([\text{H}]\text{DOG}\) uptake in the heart and striated muscle of nitrendipine compared with control SHR (Fig 4) could not have been due to differences in clearance between the groups. These results are in contrast with the similar \([\text{H}]\text{DOG}\) uptake in the spleen, which is an insulin-inert organ.

Discussion

In conformity with previous studies, nitrendipine treatment for 3 weeks significantly reduced the elevated BP in SHR.\(^{15,16}\) The salient finding in the present study is the markedly improved glucose tolerance in the nitrendipine-treated group compared with controls as evident from the significant difference in glucose disappearance rate between these groups. Unfortunately, blood samples for insulin were not drawn throughout the test because we were concerned with excessive blood loss. Nevertheless, in the presence of unchanged insulin at baseline and 30 minutes, the improved glucose tolerance in the nitrendipine group suggests an improved insulin sensitivity relative to the untreated controls. Moreover, both experimental\(^{21,22}\) and human\(^{23-25}\) studies show evidence that calcium channel blockers and specifically nitrendipine may reduce islet cell insulin secretion and the response to glucose load. This makes it unlikely that some of the improved glucose tolerance is due to increased peak insulin levels in the nitrendipine group.
The increased [3H]DOG uptake in the heart and striated muscle in nitrendipine SHR suggests that the improved glucose tolerance is the result of increased glucose uptake in this target tissue. It was shown by means of the hyperinsulinemic hyperglycemic clamp that in SHR the striated muscle is indeed the insulin-resistant organ, whereas endogenous hepatic glucose production is normally regulated. We have previously reported that [3H]DOG uptake of heart and striated muscle is reduced in SHR compared with Wistar-Kyoto rats. In the present study we have shown that [3H]DOG uptake in SHR is improved with nitrendipine. Because the nitrendipine group had significantly lower BP than the control group, a possible effect of lower BP cannot be excluded. A search of the literature provided no information on the effect of antihypertensive agents on glucose tolerance or insulin sensitivity in SHR. It would be of interest to compare the effect of vasodilator and nonvasodilator drugs on glucose tolerance and insulin sensitivity in this rat model. In this context it is noteworthy that in human hypertensive patients the medications that do not adversely affect glucose metabolism are essentially the vasodilator agents, such as α-blockers, converting enzyme inhibitors, and calcium channel blockers. It is therefore reasonable to suggest that at least part of the improvement in the glucose tolerance of nitrendipine-treated SHR may be related to nitrendipine-induced vasodilation. As transcapillary insulin delivery to tissue is critical for insulin action, it may be relevant to the structural or functional hypertension-related abnormalities and their potential reversal by treatment. Insulin resistance of both hypertension and obesity may be related to a subnormal increase in muscle blood flow in response to insulin. Vasodilators such as nitrendipine should have a beneficial effect in this regard by improving tissue insulin delivery and glucose tolerance.

In conclusion, the calcium channel blocker nitrendipine reduced BP and improved glucose tolerance in SHR by increased muscle glucose uptake, presumably secondary to its vasodilator effects.

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References

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