ORIGINAL ARTICLE

Higher glucose uptake in paralysed spastic leg

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Background: Insulin resistance and diabetes mellitus have been reported in the spinal cord injured (SCI). The group exhibits risk factors, as decreased physical activity, as well as episodes of stimulation of sympathetic nervous system below the level of lesion known to stimulate lipolysis, which in turn could induce insulin resistance. However, data are inconsistent, which might indicate the presence of protective mechanisms.

Objective: To investigate the glucose uptake in spastic paralysed SCI legs compared to able-bodied. To investigate regional differences between glucose handling in the arm and leg.

Study design: Experimental controlled study.

Settings: Institution of Clinical Neuroscience and Physiology, Spinal Injuries Unit, Sahlgrens University Hospital, Goteborg, Sweden.

Methods: Nine SCI subjects (2 C7, 7 T1–T4 ASIA A: 8, ASIA B: 1) were compared to 10 weight- and age-matched controls. Plasma flow in arm and leg was analysed by venous occlusion strain gauge plethysmography, and plasma derived from artery and veins in the arm and leg was analysed for glucose, insulin and lactate during fasting resting conditions.

Results: Glucose uptake was higher in SCI legs compared to controls. There was no difference in insulin uptake or lactate production. Plasma flow was higher in SCI legs compared to controls. Controls showed a higher glucose uptake and lactate production in arm than leg.

Conclusions: Spasticity may counteract the risk of diabetes by inducing an insulin-independent glucose uptake. The regional difference in metabolism in able-bodied make it hazardous to do generalizations to whole body metabolism from arm or leg measurements.

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Introduction

The spinal cord injured (SCI) have been reported to be at increased risk of developing diabetes mellitus¹ even though data are inconsistent. Some report impaired glucose control and insulin resistance^{2,3} whereas we have previously found normal glucose metabolism when controlling for heritage by comparison to siblings.⁴ However, the group exhibits risk factors for diabetes and insulin resistance as low physical activity and the associated risk of weight gain. Furthermore, even in the case of normal weight, we have previously shown that the group has a substantial higher proportion of fat tissue below the level of lesion.⁵ Even though the adipose tissue metabolism is normal at rest,⁵ the group is at increased risk of stimulating lipolysis owing to numerous activation of the decentralized sympathetic nervous system induced by stimuli arising below the level of lesion,⁶ stimulations that might contribute to generate insulin resistance.⁷ The discrepancy between the risk factors exhibited in

the group and the discrete findings of altered glucose metabolism might be interpreted as the presence of compensating mechanisms in the SCI body. Glucose uptake is not solely insulin mediated but also driven by active⁸ and passive muscle activity.⁹ Spasticity, the involuntary muscle activity seen in lesions of the central nervous system, is known to increase energy consumption.¹⁰ Furthermore, differences between metabolism in arm and in leg are reported in able-bodied,¹¹ and comparison of total body muscle glucose disposal rate derived from leg versus arm measurements differs by 15%.^{12,13} The loss of supraspinal control of the sympathetic nervous system affects blood pressure and vaso-regulation below the level of the lesion. However, data on blood flow to paralysed legs are inconsistent; some report a lower blood flow to paralysed legs¹⁴ whereas we previously reported an increased blood flow to legs.¹⁵

Aim

To answer the following questions:

- (1) Is involuntary muscle activity below the lesion level of importance for glucose metabolism in SCI?

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- (2) Is there a regional difference in metabolism between arms and legs in able-bodied?

Methods

Subjects

Nine SCI subjects and 10 weight- and age-matched control subjects were investigated. None in the subject groups suffered from any ongoing disease. Two SCI subjects had a lesion level of C7, the rest T3–T5. One was ASIA B, the rest ASIA A. Three subjects in the SCI group used drugs to stem urinary leakage (probanelinebromide) and to reduce spasms (baclophen). Body composition was investigated by DEXA scanning¹⁶ (Lunar DPX (L) Scanexport Medical, Helsingborg, Sweden) yielding body composition in arms, legs, trunk and head separated in fat, lean and bone mineral content. For subject characteristics see Table 1.

Experimental protocol

The subjects arrived in the laboratory at 0800 hours after an overnight fast. They were investigated in the supine resting position. A Venflon cannula (Viggo Helsingborg, Sweden) was inserted into the right radial artery for blood sampling. A blood-sampling catheter was then inserted into the left femoral vein and under fluoroscopic guidance (Seldinger technique) placed approximately 15 cm distally in the vessel. In addition, a cannula was inserted into the deep vein in the cubital fossa of the left arm and directed 5 cm proximally for venous blood sampling. Following catheterization, the subjects rested for 1 h before blood sampling was performed.

Blood flow in the right forearm and calf was measured by venous occlusion strain gauge plethysmography. Blood flow was recorded 4–5 times at the end of the resting period, and baseline values are the mean of these measurements. Blood samples were taken simultaneously in radial artery, femoral and arm veins and the samples were kept on ice and immediately centrifuged (3000 g, +4°C). Plasma was stored at –20°C until analysed. The study was approved by the Ethic Committee at Sahlgrens Academy, Goteborg, Sweden.

Analysis of samples

Glucose was estimated enzymatically (Wako Chemicals, Germany) and insulin and lactate were analysed at the Department of Clinical Chemistry (accredited according to

the Organisation for Economic Cooperation and Development (OECD) standards), University of Gothenburg, Sweden.

Calculations

Limb glucose uptake rate was calculated as

$$GLULIMB_{\text{UPTAKE}} = (GLU_{\text{ART}} - GLU_{\text{VEN}}) \times PF \mu\text{mol/ml/min/100 g}$$

Limb insulin uptake rate was calculated as

$$INSLIMB_{\text{UPTAKE}} = (INS_{\text{ART}} - INS_{\text{VEN}}) \times PF \mu\text{IU/ml/min/100 g}$$

Limb lactate production rate was calculated as

$$LACTLIMB_{\text{PRODUCTION}} = (LACT_{\text{VEN}} - LACT_{\text{ART}}) \times PF \mu\text{mol/ml/min/100 g}$$

where PF is plasma flow (ml/min/100 g) calculated as blood flow multiplied by (1–haematocrit). GLU_{ART} and GLU_{VEN} and $LACT_{\text{VEN}}$ and $LACT_{\text{ART}}$ are the arterial and venous concentration of glucose and lactate in mmol/l respectively. INS_{ART} and INS_{VEN} are the arterial and venous concentration of insulin in mIU/l.

Statistics

All values are mean with s.e.m. Comparisons between groups were analysed by Student's *t*-test for unpaired data and comparisons within groups with Student's *t*-test for paired data. $P < 0.05$ was defined as statistically significant.

Results

Glucose uptake was almost three times higher in the legs of SCI subjects compared to legs of control subjects (0.34 ± 0.08 vs $0.12 \pm 0.05 \mu\text{mol/ml/min/100 g}$, $P < 0.05$) (Table 4). The difference in glucose uptake was not due to differences in arterial concentration of glucose. Venous concentration of glucose in legs showed a tendency to be lower in SCI subjects but this did not reach statistical significance (Table 3). However, plasma flow was higher in the legs of the SCI subjects compared to controls (Table 2). The difference in glucose uptake was not due to differences in insulin uptake because there were no statistically significant differences between groups in insulin uptake (Table 4). Lactate production showed a tendency to be higher in spastic legs of SCI subjects, but this did not reach statistical significance (Table 4). Comparison of body composition in the legs showed a big difference between groups, with the lean tissue mass in SCI legs being only 2/3 of the lean tissue mass in able-bodied subjects (Table 1). Thus, the higher glucose uptake in legs of SCI subjects could not be due to a higher proportion of muscles in spastic legs.

When comparing regional metabolism within groups, we found that able-bodied subjects showed a regional difference between arm and leg with a lower glucose uptake in legs than in arms. This difference was not found in SCI subjects. The control group also showed a regional difference between arm and leg venous values and arteriovenous difference that was not seen in the SCI group (Table 3). The venous glucose concentration was higher in leg than in arm. There was a regional difference in plasma flow with a lower flow in leg than in arm in able-bodied (Table 2).

Table 1 Subject characteristics

	SCI subjects	Control subjects
N	9	10
Age, years	40.8 ± 4.3	31.9 ± 2.0
Weight, kg	71.2 ± 4.3	75.9 ± 2.3
Lean weight, kg	49.3 ± 2.7	60.2 ± 2.0**
Lean weight arms, kg	7.41 ± 0.36	7.46 ± 0.38
Lean weight legs, kg	14.17 ± 0.86	20.67 ± 0.84*

Abbreviation: SCI, spinal cord injured.

*Significant differences between groups $P < 0.05$.

**Significant differences between groups $P < 0.01$.

In line with the higher glucose uptake in arms we also found a higher lactate production in arms than in legs in able-bodied. This regional difference was not present within the SCI group (Table 4).

Discussion

The main findings of our study were the following:

- Glucose uptake is higher in paralysed, spastic legs of SCI subjects than in able-bodied during resting, supine conditions.
- Plasma flow is higher in paralysed legs of SCI subjects than in able-bodied.
- There is a regional difference in glucose uptake in able-bodied with a lower uptake in legs than in arms.
- Insulin uptake showed no regional or groupwise differences.

The finding of a higher glucose uptake in paralysed legs during supine resting condition was surprising and contradictory to the finding of no difference in resting glucose uptake between control and SCI subject in a study by Kjaer *et al.*¹⁷ It was not caused by a higher insulin uptake, because we found no difference between the groups with respect to insulin kinetics. There were differences in body composition, with a significantly lower proportion of LBM in the paralysed legs below the lesion level, a condition that might, if anything, give a lower glucose uptake. However, the finding might be misleading because investigations of the property of spastic muscle cells show that the spastic muscle cells are shorter and stiffer than normal muscle cells.¹⁸ This might indicate that the difference in body composition is not due to loss of muscle mass but shrinkage of muscle cells. Furthermore, our finding of a higher glucose uptake in paralysed spastic muscles might indicate that these muscles are more metabolically active than resting normally innervated muscles. An investigation of metabolism in patients

Table 2 Regional plasma flow (ml/min/100 g)

	Arm	Leg
SCI	2.52 ± 0.79	1.15 ± 0.16*
Control	2.49 ± 0.31	0.75 ± 0.10 ^{##}

*Significant differences between groups $P < 0.05$.

^{##}Significant differences arm–leg in control subjects $P < 0.05$ and $P < 0.01$.

Table 3 Arterial and regional venous glucose and lactate concentrations

	Arterial	Venous arm	Venous leg	AV-diff arm	AV-diff leg
Glucose SCI (mmol/l)	4.99 ± 0.17	4.81 ± 0.24	4.65 ± 0.15	0.18 ± 0.10	0.34 ± 0.08
Glucose control	5.09 ± 0.8	4.80 ± 0.06	4.92 ± 0.08 ^{##}	0.28 ± 0.08	0.17 ± 0.07 ^{##}
Lactate SCI (mmol/l)	0.71 ± 0.24	0.82 ± 0.27	0.84 ± 0.30	0.11 ± 0.04*	0.15 ± 0.05
Lactate control	0.80 ± 0.25	0.97 ± 0.32	0.90 ± 0.29	0.23 ± 0.08	0.11 ± 0.03 ^{##}

Abbreviation: AV, arteriovenous.

*Significant difference between groups $P < 0.05$.

^{##}Significant differences arm–leg in control subjects, $P < 0.05$ and $P < 0.01$.

with cerebral palsy before and after treatment with the spasmolytic drug baclophen showed a significant decrease in metabolic rate after treatment.¹⁰ This indicates that spastic muscles are not resting during resting condition; that is, spastic activity increases the non-insulin-dependent glucose uptake. In the above-mentioned study by Kjaer *et al.*, it was found that electrically induced exercise in SCI subjects increased glucose uptake more than voluntary cycling control subjects, maybe by inducing spasticity during the procedure.¹⁷

The finding of a lower glucose uptake in leg than in arm in able-bodied is in line with the previous finding of a difference in metabolism between arm and leg in the fasting state.¹⁹ It might be suggested that the difference may be due to differences in plasma flow because the cited study also showed a regional difference in plasma flow with a higher flow in arm than in leg. The same may be true for the higher glucose uptake in SCI legs compared to able-bodied.

We have previously shown that there are differences in sympathetic nervous system activity between arm and leg, with a lower noradrenaline spillover in leg compared to arm.²⁰ These differences in metabolism and neurogenic activity make it hazardous to make generalizations for the whole body from arm or leg measurements.

In summary, spasticity in SCI subjects may act as a compensating mechanism in glucose metabolism by counteracting the tendency to hyperglycaemia by a non-insulin-dependent glucose uptake in spastic muscles. In able-bodied we found a regional difference in glucose metabolism that makes generalization from arm or leg measurements hazardous.

Table 4 Regional glucose and insulin uptake and lactate production

	Uptake/production arm	Uptake/production leg
Glucose SCI ($\mu\text{mol}/\text{ml}/\text{min}/100\text{ g}$)	0.56 ± 0.20	0.34 ± 0.08*
Glucose control	0.73 ± 0.20	0.12 ± 0.05 [#]
Insulin SCI ($\mu\text{U}/\text{ml}/\text{min}/100\text{ g}$)	0.72 ± 0.40	0.75 ± 0.20
Insulin control	1.01 ± 0.84	0.40 ± 0.17
Lactate SCI ($\mu\text{mol}/\text{ml}/\text{min}/100\text{ g}$)	0.29 ± 0.10	0.18 ± 0.06
Lactate control	0.57 ± 0.19	0.08 ± 0.02 ^{##}

Abbreviation: SCI, spinal cord injured.

*Significant differences between groups $P < 0.05$.

^{##}Significant differences arm–leg in control subjects $P < 0.05$ and $P < 0.01$.

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