Does Fluoxetine Administration Influence Insulin Resistance in 90% Pancreatectomized Rats?

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This study evaluates the effect of fluoxetine (FXTN) on insulin resistance and glucose uptake by various tissues in 90% pancreatectomized (Px) and sham-operated (Sham) rats. Both the Px and Sham rats were divided into 2 groups: 1 group was given FXTN (5 mg/kg) for 8 weeks, and the other group was given a placebo. Whole body glucose disposal rates were measured using euglycemic hyperinsulinemic (EH) clamps while the rats were in an awake, unstressed, and fasting state. On the following day, all rats were intravenously injected with [1-^{14}C]2-deoxyglucose solution and killed 45 minutes later. The body weight of the FXTN group was lower than that of the placebo group in the Sham and Px rats during the first 2 weeks ($P < .05$), but there was no difference in body weight between these groups after the third week. Evidently, FXTN did not alter serum glucose levels in the Sham and Px rats. Basal serum insulin levels at EH clamp were significantly lower in the FXTN group than the placebo group in Sham rats. Whole body glucose disposal rates increased with FXTN administration in Sham rats (44.8 ± 3.4 *v* 36.4 ± 2.9 mg/kg/min) and in Px rats (33.9 ± 3.6 *v* 25.5 ± 4.1 mg/kg/min) compared with placebo administration. The glycogen content of the soleus muscle tissue was higher in the FXTN group than in the placebo group of Sham and Px rats. The dose percentage of [1-^{14}C]2-deoxyglucose uptake by soleus muscle tissue was higher in the FXTN group than in the placebo group of Sham and Px rats. In conclusion, (1) FXTN improves insulin sensitivity beyond the effect mediated through weight loss and (2) the effect of FXTN on insulin sensitivity may be achieved by increased glucose uptake and glycogen synthesis in the soleus muscle tissue.

DEVELOPMENT OF TYPE 2 diabetes is strongly associated with the insulin resistance syndrome, comprising hypertension, dyslipidemia, abdominal obesity, and hyperinsulinemia.[1] Multiple neuroendocrine dysregulation, particularly on decreased activity of serotonin, might be an essential pathogenic factor for this syndrome.[2] As serotonin is an appetite-modulating neurotransmiter, it has a potent anorectic action.[2] Serotonin and its receptors are found in neurons projecting from the raphe nucleus to the hypothalamus and cortex, especially in the paraventricular nucleus (PVN), arcuate nucleus (ARC), and ventromedial nucleus (VMN).[2] High levels of serotonin in hypothalamus cause intense carbohydrate aversion, reduce feeding, and increase energy expenditure.[3] Conversely, the blockage of serotonin synthesis or the destruction of serotonin neuron induces hyperplasia and increases hypothalamic neuropeptide Y (NPY) values.[4]

Fluoxetine (FXTN) has antidepressive and appetite reduction effects.[5] FXTN specifically inhibits serotonin uptake in vitro and in vivo and results in increased synaptic concentrations of serotonin.[3,4] There is extensive functional evidence for enhanced serotonergic tone after FXTN administration. Some studies showed that serotonin has influenced numerous bodily functions controlled by the brain.[6-8] Physiologic changes by FXTN administration has been reported to promote weight loss and improve glycemic control in obese diabetic patients.[6,7] Insulin resistance contributes to the metabolic defects in type 2 diabetes mellitus. Anorectic agents have been shown to improve insulin action in type 2 diabetes, irrespective of weight reduction.[9-12] O'Kane et al[12] suggested that FXTN improved glycemic control by reducing carbohydrate consumption. However, the mechanism by which FXTN may enhance insulin sensitivity is also not clear. The purpose of this study was to determine whether FXTN administration affects insulin resistance and glucose transport into different organs in sham-operated (Sham) and 90% pancreatectomized (Px) rats.

MATERIALS AND METHODS

Animals

Thirty-two male Sprague Dawley (SD) rats weighing 171.1 ± 7.6 g were anesthetized with ketamin, and 90% of their pancreas was removed using the technique of Hosokawa et al.[13] The residual pancreas was anatomically well defined, being the tissue within 2 mm of the common bile duct and extending from the duct to the first part of the duodenum. The Px rats show characteristics of mild type 2 diabetes. Twenty-six male SD rats received a sham pancreatectomy that consisted of disengaging the pancreas from the mesentery and gently rubbing it between the fingers. The Sham rats did not have any symptoms of diabetes. After surgery, the animals were allowed free access to standard laboratory chow (Sam Yang Co, Kangwon-Do, Korea) and water. Within the group of Px rats, those with serum glucose levels less than 9.4 mmol/L were eliminated after 2 weeks of surgery.

Both of the Px and Sham rats were divided 2 groups: 1 group was given FXTN and the other group given a placebo. Rats in FXTN groups orally received 5 mg of fluoxetine-HCl (Eli Lilly, Indianapolis, IN) per 1 kg body weight every day for 8 weeks, and rats in the placebo groups were given an equivalent volume of mint-flavored water. Serum glucose levels, food intake, and body weight were measured weekly.

Euglycemic Hyperinsulinemic Clamp

Indwelling catheters were inserted into the jugular vein and carotid artery during the seventh week of FXTN and placebo administration.[14] After 5 to 6 days, euglycemic hyperinsulinemic (EH) clamp studies

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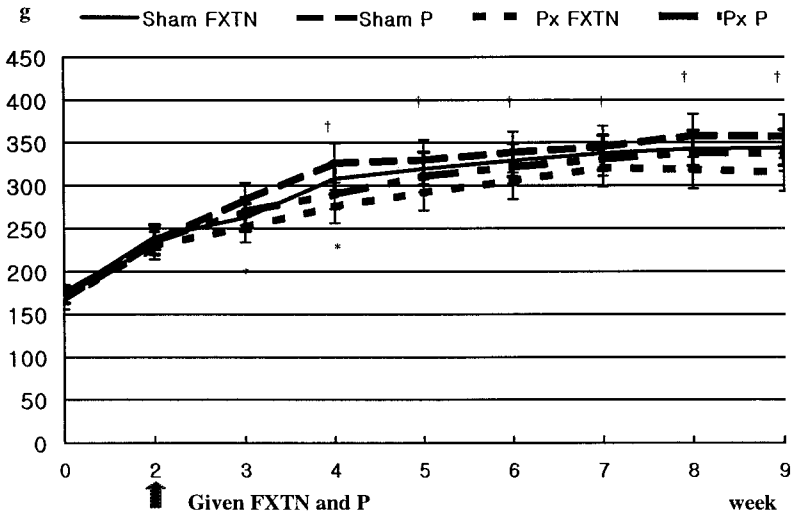

Fig 1. Weekly changes of body weight with FXTN and placebo administration in Px and Sham rats during an entire experimental period. Values are the mean ± SD. Body weight was measured every Friday at 10 AM after overnight fasting, n = 13 for all groups. FXTN, fluoxetine; P, placebo; Sham, sham-operated rats; Px, 90% pancreatectomized rats. *FXTN group is significantly lower than placebo at $\alpha = 0.05$. †Sham group is significantly different from the Px group at $\alpha = 0.05$.

were performed on the rats in an awake, unstressed, and fasting state. Hyperinsulinemia was achieved with a constant infusion of human insulin (12 mU/kg/min), and euglycemia was maintained at a variable rate of 25% glucose solution infusion with adjustment every 10 minutes according to serum glucose levels.[15] Total glucose infused equals total glucose disposed in the tissues. The glucose disposal rate was calculated and expressed in terms of milligrams of glucose/1 kg body weight/minute. The glucose disposable rate is an index of whole-body response to exogenous insulin.

Serum glucose levels were analyzed with a Glucose Analyzer II (Beckman, Palo Alto, CA). Serum insulin levels were measured by radioimmunoassay (Linco Research, St. Charles, MO).[16]

Infusion Study of [1-^{14}C]2-Deoxyglucose

After the EH clamp study, the rats ingested food and water freely for 6 hours, and they were then deprived of food for 12 hours. [1-^{14}C]2-deoxyglucose solution was administered simultaneously as an intravenous bolus in the jugular vein of the rats followed by a flush of heparinized saline. The injection solution contained [1-^{14}C]2-deoxyglucose (51.1 mCi/mmol, New England Nuclear, Boston, MA) at a dose of 1 μCi/100 g body weight, 0.9% NaCl, and 5.1 mmol/L glucose buffered to pH 7.35 with 10 mmol/L N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid.[17] Forty-five minutes later, the rats were killed by decapitation. Brain, heart, soleus and quadricep muscles, and epididymal fat pad were rapidly dissected, weighed, and frozen in liquid nitrogen. Tissues were stored at -70°C until further analysis was performed.

Biochemical Measurement

Tissues from the liver, muscle, whole brain, epididymal fat pad, and heart were homogenized with a phosphate buffer and centrifuged at 3,000 rpm for 10 minutes. Aliquotes were taken, and the radioactivity of ^{14}C was measured as counts per minute (cpm). Uptake of [1-^{14}C]2-deoxyglucose was used for determining glucose uptake in organ tissues and was expressed as percentage of injected dose/gram of each tissue.[18] To determine the glycogen content in the liver and skeletal muscle tissues, these tissues were homogenized and deproteinized with 1.5 N perchloric acid. The glycogen content was calculated from glucose concentrations derived from glycogen hydrolyzed by α-amyloglucosidase in an acid buffer.[19] Triglyceride in skeletal muscles was extracted with a chloroform-methanol (2:1 vol/vol) solution, and the triglyceride was resuspended in pure chroloform.[20] Triglyceride concentration in the suspension was determined using a Trinder kit (Sigma, St Louis, MO). Each biochemical measurement was performed in duplicate.

Statistical Analysis

All results are expressed as mean ± SD. Statistical analysis was performed using the SAS statistical analysis program (SAS Institute, Cary, NC.[21] Comparison within groups was performed by 2-way analysis of variance (ANOVA) followed by Tukey test for multiple comparisons. Differences with a P less than .05 were considered statistically significant.

RESULTS

Figure 1 illustrates the changes of body weight during the experimental periods. Body weight was lower during the first 2 weeks of FXTN treatment in Px and Sham rats compared with placebo treatment ($P < .05$). However, body weight between the FXTN and placebo groups was the same after the third week. Body weight gain reflected food intake. Food intake was lower in the FXTN groups than the placebo group by 3.3 ± 0.8 g in both Sham and Px rats during the first 2 weeks (Table 1). After the third week, average daily food intake did not differ between the FXTN and placebo groups. The body weight of the Px rats was significantly lower than those of the Sham rats during the entire period ($P < .05$). However, average daily food intake during the experimental periods did not differ between Sham and Px rats (25.6 ± 5.3 g *v* 24.7 ± 6.7 g).

Figure 2 shows the changes of serum glucose levels during the experimental periods. Serum glucose levels were higher in the Px rats than in the Sham rats. FXTN did not significantly affect serum glucose levels in Px and Sham rats during the experimental periods. Sham rats with FXTN administration had lower serum insulin than those with placebo, but FXTN did not significantly lower serum insulin levels in the Px rats (Table 1). Serum insulin levels were lower in Px rats than Sham rats regardless of FXTN and placebo administration.

Table 2 illustrates the glucose disposal rate and serum glucose and insulin levels at the EH clamp. The glucose disposal rate was lower in the Px groups than in the Sham groups ($P <$ .05). FXTN improved glucose disposal rate in the Sham rats

Table 1. Body Weight and Serum Glucose and Insulin Concentrations Before and After the Experimental Periods (mean ± SD)

Parameter	Sham		Px	
	FXTN (n = 13)	Placebo (n = 13)	FXTN (n = 13)	Placebo (n = 13)
Initial body weight (g)	173.7 ± 6.6	168.0 ± 16.2	168.0 ± 16.3	172.9 ± 10.3
Body weight at the 2nd week (g)	263 ± 17.4	283 ± 16.7*	251.7 ± 21.1†	270 ± 18.8*†
Final body weight (g)	344 ± 21	357 ± 25	315 ± 31†	337 ± 33†
Average food intake from the 1st to the 2nd week (g)	20.6 ± 2.5	17.2 ± 2.9*	19.7 ± 2.6†	16.4 ± 3.4*†
Average food intake from the 3rd to the 8th week (g)	26.5 ± 4.8	26.7 ± 5.9	25.6 ± 5.7	25.8 ± 5.5
Initial serum glucose (mmol/L)	7.4 ± 0.7	7.2 ± 0.7	11.8 ± 4.5‡	12.5 ± 3.8‡
Final serum glucose (mmol/L)	7.4 ± 0.2	7.1 ± 0.4	12.9 ± 3.6‡	14.4 ± 4.5‡
Initial serum insulin (pmol/L)	721 ± 119	703 ± 123	288 ± 116‡	294 ± 95‡
Final serum insulin (pmol/L)	515 ± 118	747 ± 138§	261 ± 101‖	358 ± 107§‖

Abbreviations: FXTN, fluoxetine; Sham, sham-operated rats; Px, 90% pancreatectomized rats.

*Significantly different *v* FXTN; †significantly different *v* Sham by Tukey test, $P < .05$; ‡significantly different *v* Sham by Tukey test, $P < .001$; §significantly different *v* FXTN; ‖significantly different *v* Sham by Tukey test, $P < 0.01$.

and the Px rats. Basal serum glucose levels at the EH clamp were higher in the Px rats than in the Sham rats ($P < .001$). However, the effect of FXTN was minimal on basal serum glucose levels. Serum glucose levels at steady-state of the EH clamp maintained euglycemia in all groups. Basal serum insulin levels at the EH clamp were affected by diabetic status and FXTN administration. They were lower in the Px rats than in the Sham rats ($P < .01$). They were significantly lower in the FXTN group than the placebo group in Sham rats ($P < .01$), and they showed the same trend in Px rats, but they were not significant. Steady-state serum insulin levels were 5 to 6 times higher than serum insulin levels at baseline.

Table 3 shows glycogen content in the liver, soleus muscle, and quadriceps muscle and triglyceride content in soleus and quadricep muscles. Diabetic status and FXTN administration did not influence liver glycogen contents. Glycogen deposits in the soleus muscle were affected by FXTN administration and diabetic status. FXTN increased glycogen deposit more than placebo in the soleus muscle of Sham and Px rats ($P < .05$). Sham rats administered FXTN had more glycogen deposits in the soleus muscle than Px rats administered FXTN ($P < .05$). Glycogen deposits in the quadricep muscle had the same trend as those in the soleus muscle, but it was not statistically significant. Triglyceride content in the soleus muscle showed an opposite direction of glycogen. The triglyceride content decreased with FXTN administration in Sham and Px rats compared with placebo. However, triglyceride content in the quadriceps muscle was not affected by diabetic status and FXTN administration.

The dose percentage of [1-^{14}C]2-deoxyglucose uptake by different organ tissues is given in Table 4. Px rats had 8.5% to 34.8% lower glucose uptake in all of the different tissues except the epididymal fat pad compared with Sham rats. Brain and heart tissues showed a minimal difference of glucose uptake with diabetic status. FXTN did not affect glucose uptake by the whole brain, and the uptake tended to be lower in Px rats ($P = .08$). Glucose uptake by the soleus muscle was influenced by diabetic status and FXTN administration ($P < .05$). The glucose uptake was higher with FXTN administration than placebo in Sham and Px rats, and the uptake in Sham rats was higher than that in Px rats with and without FXTN. The glucose uptake by the soleus muscle showed the same trend as glycogen

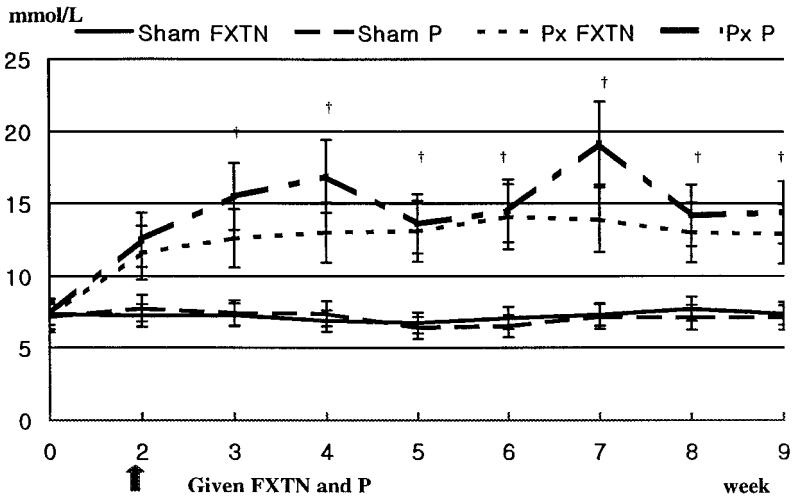

Fig 2. Weekly changes of serum glucose concentrations with FXTN and placebo administration in Px and Sham rats during an entire experimental period. Values are the mean ± SD. Serum glucose concentrations were measured every Friday at 10 AM after overnight fasting, n = 13 for all groups. FXTN, fluoxetine; P, placebo; Sham, sham-operated rats; Px, 90% pancreatectomized rats. †Sham group is significantly different from the Px group at $\alpha = 0.001$.

Table 2. Glucose Disposal Rate and Serum Glucose and Insulin Concentrations at EH Clamp (mean ± SD)

Parameter	Sham		Px	
	FXTN (n = 12)	Placebo (n = 13)	FXTN (n = 12)	Placebo (n = 12)
Glucose disposal rate (mg/kg/min)	44.8 ± 3.4	36.4 ± 2.9*	33.9 ± 3.6†	25.6 ± 4.1*†
Basal glucose (mmol/L)	7.3 ± 0.6	7.1 ± 1.0	13.1 ± 2.4‡	14.3 ± 3.3‡
Steady-state glucose (mmol/L)	5.4 ± 0.2	5.3 ± 0.1	5.2 ± 0.1	5.4 ± 0.3
Basal insulin (pmol/L)	545 ± 179	774 ± 182§	280 ± 113‖	354 ± 122§‖
Steady-state insulin (pmol/L)	3,120 ± 712	3,328 ± 812	3,140 ± 624	3,116 ± 756

Abbreviations: FXTN, fluoxetine; Sham, sham-operated rats; Px, 90% pancreatectomized rats.

*Significantly different *v* FXTN; †significantly different *v* Sham by Tukey test, $P < 0.05$; ‡significantly different *v* Sham by Tukey test, $P < .001$; §significantly different *v* FXTN; ‖significantly different *v* Sham by Tukey test, $P < .01$.

content in the soleus muscle. The quadricep muscle had the same tendency of glucose uptake as the soleus muscle. FXTN did not show any effect on the uptake by the quadricep muscle, but diabetic status did. The glucose uptake by the epididymal fat pad was lower with FXTN administration than placebo in Sham and Px rats. Diabetic status and FXTN administration did not affect the glucose transport of the heart and liver.

DISCUSSION

The present study demonstrated that FXTN improved insulin resistance independent of weight changes in rats. Improved insulin resistance with FXTN administration was partially explained by increased glucose uptake by soleus muscle and decreased uptake by the epididymal fat pad. The means by which the serotonin reuptake inhibitor increased the glucose uptake and glycogen synthesis in muscle and decreased glucose uptake in the epididymal fat pad was not determined.

In our study, the body weight of rats given a moderate dosage of FXTN was lower than that of those given a placebo for the first 2 weeks in normal and diabetic rats. However, the body weight did not differ between FXTN and placebo groups after the third week. Studies have shown that FXTN causes weight loss in obese patients.[22,23] However, some studies reported that chronic administration of FXTN caused weight gains after 2 to 3 weeks in animals.[4] This could be explained by the report that rats treated with FXTN alone resumed eating by the end of the 6-hour period, although FXTN inhibits serotonin uptake for more than 24 hours. The compensatory reduction in serotonin synthesis and in serotonin neuron firing that occurred when uptake was inhibited probably reduced the activation of postsynaptic serotonin receptors responsible for the initial anorectic effect.[4,23]

It is known that glucose utilization is not affected by plasma glucose or insulin concentrations except under conditions of severe hypoglycemia.[24,25] However, several studies[26-29] have shown that regional cerebral glucose utilization was altered by some conditions, such as hyperinsulinemia,[26] mental stress,[27,28] and drug administration, such as cocaine.[29,30] Porrino et al[29] showed that FXTN administration altered rates of local cerebral glucose utilization in rats in a dose-dependent manner. More than 10 mg FXTN administration/kilogram body weight decreased glucose utilization in locomotor behavior, as well as widespread reductions in rats' metabolic activity in the brain area including the raphe nuclei, dorsal, and ventral striatum, amygdala, hippocampus, limbic cortex, and thalamus. However, Frick et al[30] showed that even a high dosage (25 mg/kg body weight) of FXTN administration produced the smallest overall effect in the lateral geniculate, hippocampus, and parietal hypothalamus. In our study, a 5-mg administration of FXTN/kilogram body weight did not change glucose uptake by the whole brain. The dosage of FXTN may be too low to show the alteration of glucose uptake even by the brain region, and we did not observe regional glucose uptake.

Other serotonin agonist agents, such as m-CPP and WF-31, are similar to FXTN in metabolic activity.[29] They also decreased glucose utilization in specific regions of the brain, but the change of their glucose utilization was different. Unlike the FXTN effect, WF-31 produced more discrete changes in metabolic activity that was localized within the raphi nuclei and in portions of the hippocampal formation.[29,30]

It is unknown how FXTN decreases body weight and insulin resistance. It has been reported that FXTN administration reduced food intake leading to weight reduction in animal and human studies.[6,7] FXTN improved insulin resistance in animal and human studies, and some studies explained this phenomenon in terms of weight reduction. But other studies show that

Table 3. Liver Glycogen and Glycogen and Triglyceride in Soleus and Quadricep Muscles (mean ± SD)

Parameter (mg/g tissue)	Sham		Px	
	FXTN (n = 12)	Placebo (n = 13)	FXTN (n = 12)	Placebo (n = 12)
Liver glycogen	40.7 ± 11.7	41.9 ± 10.0	38.3 ± 7.9	38.0 ± 9.8
Soleus muscle glycogen	4.8 ± 0.8	3.1 ± 0.7*	3.8 ± 0.8†	2.6 ± 1.0*
Quadricep muscle glycogen	3.6 ± 0.9	2.7 ± 0.8	3.3 ± 1.1	2.3 ± 0.6
Soleus muscle triglyceride	1.9 ± 1.0	3.7 ± 1.1*	3.3 ± 1.1†	4.9 ± 1.2*
Quadricep muscle triglyceride	2.8 ± 1.3	4.0 ± 1.6	3.4 ± 1.1	3.8 ± 1.4

Abbreviations: FXTN, fluoxetine; Sham, sham-operated rats; Px, 90% pancreatectomized rats.

*Significantly different *v* FXTN; †significantly different *v* Sham by Tukey test, $P < .05$.

Table 4. The Percentage of [1-^{14}C]2-Deoxyglucose Uptake by Each Organ Tissue (mean ± SD)

Parameter (% of injected dose per g tissue)	Sham		Px	
	FXTN (n = 12)	Placebo (n = 13)	FXTN (n = 12)	Placebo (n = 12)
Brain	0.263 ± 0.072	0.272 ± 0.051	0.246 ± 0.082	0.240 ± 0.075
Soleus muscle	0.188 ± 0.042	0.146 ± 0.049*	0.132 ± 0.038†	0.096 ± 0.044*†
Quadricep muscle	0.108 ± 0.051	0.102 ± 0.046	0.076 ± 0.034†	0.061 ± 0.038†
Liver	0.166 ± 0.034	0.154 ± 0.031	0.142 ± 0.042	0.128 ± 0.046
Heart	0.842 ± 0.128	0.854 ± 0.146	0.724 ± 0.112	0.828 ± 0.166
Epididymal fat	0.012 ± 0.004	0.017 ± 0.005*	0.019 ± 0.004†	0.021 ± 0.005*

Abbreviations: FXTN, fluoxetine; Sham, sham-operated rats; Px, 90% pancreatectomized rats.
*Significantly different *v* FXTN; †significantly different *v* Sham by Tukey test, $P < .05$.

improved insulin sensitivity was independent of weight reduction with FXTN. In our study, FXTN did not lower body weight, but it improved the whole body glucose disposal rate in the insulin-resistant animal. Thus, insulin resistance can be associated with brain action influenced by serotonergic tone.

FXTN increased serotonin in the hypothalmus, and serotonin modulates NPY activity,[31] which was 1 of the most powerful appetite stimulants, inducing striking carbohydrate and fat selective hyperphasia.[32] NPY and serotonin neurons are anatomically closely connected. Serotonin inhibited NPY synthesis and NPY secretion, which was reduced in the PVN of the hypothalamus. Meanwhile, insulin may inhibit NPY neurons in the ARC under normal conditions, and some studies have found insulin to alter NPY and NPY mRNA levels.[33]

Serotonin may stimulate the release of corticotropin-releasing factor, which could modulate NPY activity either directly or through glucocorticoids, which stimulate NPY in some systems.[4,32,34] Either of these 2 factors could potentially mediate the effects of FXTN on NPY. Insulin levels were reduced in the FXTN-treated animals, but this was matched in the pair-fed groups and therefore appeared to have been due to reduced nutrient intake. This may be associated with increased insulin sensitivity. Reduction of the NPY concentration in PVN and a decrease of glucocorticoids can influence appetite and glucose metabolism, leading to weight reduction and the improvement of insulin resistance.

In conclusion, this study suggests that FXTN does reduce insulin resistance without lowering body weight. Increased insulin sensitivity is associated with increased glucose transport to, and storage of glycogen, in the soleus muscle.

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