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Fatty Acid Translocase (Cd36), Energy Substrate Utilization, and Insulin Signaling in Brown Adipose Tissue in Spontaneously Hypertensive Rats

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Abstract : Brown adipose tissue (BAT) plays an important role in lipid and glucose metabolism in rodents and possibly also in humans. Recently, using systems genetics approach in the BAT from BXH/HXB recombinant inbred strains, derived from the SHR (spontaneously hypertensive rat) and BN (Brown Norway) progenitors, we identified Cd36 (fatty acid translocase) as the hub gene of co-expression module associated with BAT relative weight and function. An important aspect of BAT biology is to better understand the mechanisms regulating the uptake and utilization of fatty acids and glucose. Accordingly, BAT function in the SHR that harbors mutant nonfunctional Cd36 variant (hereafter referred to as SHR-Cd36$^{-/-}$) was compared with SHR transgenic line expressing wild type Cd36 under control of a universal promoter (hereafter referred to as SHR-Cd36$^{+/+}$). BAT was incubated in media containing insulin and 14C-U-glucose alone or 14C-U-glucose together with palmitate. Incorporation of glucose into BAT lipids was significantly higher in SHR-Cd36$^{+/+}$ versus SHR-Cd36$^{-/-}$ rats when incubation media contained glucose alone (SHR-Cd36$^{-/-}$ 591 ± 75 vs. SHR-Cd36$^{+/+}$ 1036 ± 135 nmol/gl./2h; $P < 0.005$). Adding palmitate into incubation media had no effect in SHR-Cd36$^{-/-}$ rats but significantly reduced glucose incorporation into BAT lipids in SHR-Cd36$^{+/+}$ (SHR-Cd36$^{-/-}$ 543 ± 55 vs. SHR-Cd36$^{+/+}$ 766 ± 75 nmol/gl./2h; $P < 0.05$ denotes significant Cd36 x palmitate interaction determined by two-way ANOVA). This Cd36-dependent reduced glucose uptake in SHR-Cd36$^{+/+}$ BAT was likely secondary to increased palmitate incorporation and utilization due to the presence of wild type Cd36 fatty acid translocase in transgenic rats. This possibility is supported by increased incorporation of 14C-U-palmitate into BAT lipids in the presence of both palmitate and glucose in incubation media (palmitate alone: SHR-Cd36$^{-/-}$ 870 ± 21 vs. SHR-Cd36$^{+/+}$ 899 ± 42; glucose+palmitate: SHR-Cd36$^{-/-}$ 899 ± 47 vs. SHR-Cd36$^{+/+}$ 1460 ± 111 nmol/palm./2h; $P < 0.05$ denotes significant Cd36 x glucose interaction determined by two-way ANOVA). It is possible that addition of glucose into the incubation media increased palmitate incorporation into BAT lipids in SHR-Cd36$^{+/+}$ rats because of glucose availability for glycerol phosphate production and increased triglyceride synthesis. These changes in glucose and palmitate incorporation into BAT lipids were associated with significant differential expression of Irs1, Irs2, Slc2a4 and Foxo1 genes involved in insulin signaling and glucose metabolism only in SHR-Cd36$^{+/+}$ rats which suggests Cd36-dependent effects on insulin action. In conclusion, these results provide compelling evidence that Cd36 plays an important role in BAT insulin signaling and energy substrate utilization.

Keywords : brown adipose tissue, Cd36, energy substrate utilization, insulin signaling, spontaneously hypertensive rat
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