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Abstract

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“The Marathon Mouse and Genetically Engineered Endurance”

The nuclear hormone receptor family controls broad aspects of body physiology by modulating the activity of target genes.

One such receptor termed, PPARdelta, has generated particular interest because of its ability to promote oxidative metabolism and suppress inflammation. The anti-inflammatory effects of PPARdelta suggest that it may be an effective therapeutic target in the control of atherosclerosis as well as inhibiting other inflammatory associated diseases. However, evidence for the beneficial action of PPARdelta specific drugs in suppression inflammation in vivo or promoting metabolic changes in vivo, are still under investigation. Recent studies describing PPARdelta action in adipose tissue and muscle will be described.

In regards to oxidative metabolism, mice expressing a PPARdelta transgene in muscle, show increased generation of type I (slow-twitch) fibers associated with mitochondrial proliferation and increased respiration. While these animals eat normal amounts of food, they are resistant to weight gain when placed on a high fat diet. These animals, also known as "Marathon" mice exhibit the remarkable ability to run twice the distance of the non-transgenic littermates. Marathon mice are fertile and transfer running capacity to progeny.

We are developing small molecule orally active "tool" drugs that are able to trigger the PPARdelta switch. We are studying the ability of these drugs to moderate inflammation, protect against weight gain on high fat diets, and to potentially alter muscle physiology.