



Figure 1. Effect of dexamethasone (DEX) on muscle protein synthesis in adult and old rats; protein synthesis was measured in vivo (*gastrocnemius* muscle) or in vitro (*epitrochlearis* muscle) (* $P < 0.01$ Student's t -test. FSR: fractional synthesis rate.

milk protein more than their TL/TL half sisters. Carriers of the BL gene also produced more fat in their milk.

The frequency of the BL/TL genotypes in the tested population shows that mutation carriers are not eliminated from the population through natural selection; therefore, their immune system functions as well as that of the wild-type animals.

The BL allele appears to be a good tool for marker-assisted selection in genetic improvement of milk production in cattle.

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Skeletal muscle protein synthesis in adult and old rats. I. Savary, D. Dardevet, E. Debras, C. Sornet, P. Patureau Mirand, J. Grizard (Laboratoire croissance et métabolisme des herbivores et Unité d'étude du métabolisme azoté, Inra, Theix, 63122 Saint-Genès-Champanelle, France)

The aim of this study is to determine whether or not glucocorticoids are involved

in muscle wasting during ageing. Indeed, these hormones are known to induce muscle atrophy by inhibiting protein synthesis and promoting protein breakdown. Adult (6–8 months) and old (18–24 months) rats received dexamethasone (DEX) in their drinking water for 5 days (old rats) and 6 days (adult rats) in order to generate a similar atrophy of *epitrochlearis* and *gastrocnemius* muscles in both groups (old rats are more sensitive to DEX than adult rats). As DEX decreased food intake, all groups were pair fed to DEX-treated old rats. The DEX treatment was associated with a strong increase in insulinaemia and glycaemia at both ages.

Protein synthesis of *gastrocnemius* muscle was assessed in vivo by a flooding dose of ^{13}C valine 50 min before slaughter. DEX induced a decrease in protein synthesis in vivo in adult and old rats but this decrease was greater in old rats (–56.3 % for old rats, –34.5 % for adult rats $P < 0.01$; figure 1).

To further analyse this greater inhibition of protein synthesis to DEX in old rats, protein synthesis was measured in isolated epitrochlearis incubated in the presence of ^{14}C phenylalanine. The effect of DEX in this case was a decrease in protein synthesis in old rats but not in adults, suggesting an intrinsic change during ageing in the effect of DEX on skeletal muscle.

Since DEX is a potent diabetogenic factor, *in vitro* protein synthesis was also measured in the presence of insulin (30 nM). DEX-treated rats showed an insulin-resistant state. This phenomenon was greater in old than in adult rats (–26 % DEX-treated versus control adult rats, –49 % DEX-treated versus control old rats, $P < 0.01$). Note that these results obtained *in vitro* in the presence of insulin are in total accordance with those obtained *in vivo* (figure 1).

If we consider all these findings, we can conclude that a higher responsiveness to glucocorticoids along with the establishment of a greater insulin-resistant state may explain muscle protein wasting during ageing.

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The rapamycin-sensitive pathway is not involved in the impairment of skeletal muscle protein synthesis observed in diabetes-associated or glucocorticoid-induced insulin resistance. K. Grzelkowska, D. Dardevet, C. Sornet, M. Balage, J. Grizard (Unité d'étude du métabolisme azoté, Inra, Theix, 63122 Saint-Genès-Champanelle, France)

It has been shown that the PI-3 kinase/ $p70^{\text{S6K}}$ signalling pathway was involved in insulin-regulated muscle protein synthesis (Dardevet et al., *Endocrinology* 137 (1996) 4087–4094). The aim of the present study was to examine the possible contribution of the $p70^{\text{S6K}}$ pathway in the impairment of skeletal muscle protein synthesis observed in

the case of insulin resistance. We investigated the effect of rapamycin on insulin-stimulated protein synthesis in rat epitrochlearis muscle *in vitro*. Rapamycin is considered as a 'specific' inhibitor of transduction pathways including $p70^{\text{S6K}}$ (Brown et al., *Nature* 377 (1995) 441–446). The $p70^{\text{S6K}}$ protein level and $p70^{\text{S6K}}$ activity were analysed by western blotting and the immune complex kinase assay. Two models of insulin resistance were used: streptozotocin (STZ)-diabetic rats (3 days intravenous injection of 110 mg STZ/kg b.w.) and dexamethasone (DEX)-treated rats (2.19 mg DEX/kg b.w. per day, given via drinking water, for 4 days).

When compared to appropriate controls, the effect of insulin on muscle protein synthesis *in vitro* was decreased by 40 and 60 % in DEX-treated and STZ-diabetic rats, respectively. In the presence of rapamycin, insulin-stimulated protein synthesis was diminished but not abolished, suggesting that insulin signalling in muscle involves both rapamycin-sensitive and rapamycin-insensitive pathways. The relative contribution of each pathway was not modified by DEX (rapamycin reduced insulin action by 33 and 37 % in control and DEX-treated rats, respectively). Rapamycin-dependent mechanisms were relatively more important in STZ rats (insulin action was reduced by rapamycin by 36 and 68 % in control and diabetic rats, respectively). The $p70^{\text{S6K}}$ protein level and basal $p70^{\text{S6K}}$ activity were not altered in any model. Whereas insulin caused an activation of $p70^{\text{S6K}}$ in STZ-diabetic rats, no stimulatory effect was observed in muscles of DEX-treated rats. On the basis of the present results we concluded that, even though an alteration of rapamycin-dependent elements occurs, the rapamycin-sensitive pathway does not account for the impairment of muscle protein synthesis observed in the case of DEX-induced or diabetes-associated insulin resistance.