ABSTRACT

Nutrient excess has overpowered the conservatory mechanisms letting metabolic diseases burgeon. Diabetes and disabilities associated with insulin resistance have reached alarming proportions claiming more lives, health budget and economic drain. S6K1 has been attributed to be the major propagator of insulin resistance with knockdown models showing marked reduction in propensity for age-related and diet-related pathologies along with outstanding insulin sensitivity. Some of the major regulators of metabolic control like AMPK, GSK3beta are known to modulate S6K1 to fine tune signals for metabolic adjustments. Major drawback posed towards meaningful inhibition of this enzyme to ameliorate insulin resistance and age related infirmities is by the dysregulation of its upstream kinase and much reputed regulator mTORC1. Many potent and specific inhibitors of this kinase have revealed functions that preclude the mechanism followed by rapamycin which had long been touted as the reliable and specific inhibitory agent of mTORC1. Hypoglycemics like metformin, troglitazone and naturals compounds like caffeine have been observed to inhibit S6K1 and many other effectors of mTORC1 without considerable involvement of mTORC1 per se. This assumed even more importance for investigation in light of studies that have implicated mTOR independent influence of enzymes, AMPK, DRAK2 and GSK3beta on S6K1. In fact, much discordance can be discerned in the reported effect of these kinases on mTORC1 per se in the past with the individual influence they have on S6K1, presented lately.

We provide evidence that AMPK actually stimulates S6K1 irrespective of its effect on mTORC1 and similar to DRAK2 acts on S6K1 in a manner that is mechanistically opposite to caffeine inhibition of this kinase. Further,
caffeine, a natural hypoglycemic differs from metformin and even rapamycin in its mechanism of action and actually inhibits S6K1 through mTORC2. Also, GSK 3 beta stimulated Ser 394 is not pre-requisite for mTORC1 to phosphorylate and activate S6K. On the contrary T412 is required for GSK 3 beta to increase phosphorylation at Ser 394 with even phosphomimicked mutants of T412 showing increase in activation by GSK3beta, making GSK3 beta an additional regulatory element to promote S6K1 activity. Our study addresses many loopholes and paves way towards understanding of S6K1 regulation by these players in light of mTORC2 in place of mTORC1. Our results lends support to development of drugs that differentially target the two mTOR complexes in order to modulate S6K1 activity keeping the burden of side-effects minimal.