GHRELIN AND DES-ACYL GHRELIN INDUCE MURINE C2C12 MYOBLASTS DIFFERENTIATION AND FUSION INTO MYOTUBES

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Ghrelin is an acylated peptidyl gastric hormone stimulating appetite, adiposity and growth hormone (GH) release, through activation of GH secretagogue receptor type 1a (GHSR-1a). Ghrelin exists also in a more abundant, non-acylated form, named des-acyl ghrelin, which does not bind GHS-R1a and is devoid of any endocrine activity. It is becoming apparent that des-acyl ghrelin has a metabolic valence: it acts on pancreas, liver and adipose tissue, to control energetic homeostasis through receptors which may, or may not, be shared by ghrelin, and that are currently unknown yet. Also, des-acyl ghrelin was demonstrated to stimulate differentiation in pre-adipocytic cells and osteoblasts, effect which was shared with ghrelin. Presently, we do not know whether myoblasts may be sensitive to acylated ghrelin or its des-acyl counterpart; in particular, it would be interesting to known whether they affect myoblasts ability to differentiate and regenerate injured/lost muscle fibers. In this study we investigated whether des-acyl ghrelin and ghrelin control myoblasts capacity to proliferate or differentiate into myotubes by using the murine skeletal myoblastic cell line C2C12. Both ghrelin and des-acyl ghrelin stimulated proliferating myoblasts to differentiate and to fuse into multinucleated myotubes, as testified by an increased production of myogenin, of myosin heavy chain and a decreased ^{3}H-thymidine incorporation. Such process involved activation of p38 kinase. Consistently, both ghrelin and des-acyl ghrelin inhibited C2C12 proliferation. Moreover, the ectopic expression of ghrelin in C2C12 enhanced differentiation and fusion of the myoblasts. Competition binding studies with ^{125}I-ghrelin demonstrated that a common site is recognized with high-affinity by both acylated and des-acylated ghrelin (no GHS-R1a expression could be detected) and suggested that the described activities are likely mediated by this yet unidentified receptor.