Isoproterenol Activates Extracellular Signal-Regulated Protein Kinases in Cardiomyocytes Through Calcineurin

To the Editor:

Zou et al1 reported recently that isoproterenol activates extracellular signal-regulated protein kinases (ERK) in cardiomyocytes through calcineurin. The results mediated by β-adrenergic receptors (β-AR) were convincing in neonatal cardiomyocytes but might not be applicable to adult cardiomyocytes, which undergo pathological hypertrophy. Communal et al2 demonstrated that ERK is not activated by isoproterenol using adult rat ventricular myocytes kept in culture for 16 hours. Recently, we made a similar observation using adult cardiomyocytes cultured for 48 hours.3 It is clear that signal transduction mediated by β-AR and G, and G, coupling to β-AR subtypes differs between adult and neonatal cardiomyocytes. The dosages of isoproterenol used to induce hypertrophy in neonatal cardiac myocytes in the study of Zou et al induces cardiomyocyte death by apoptosis rather than hypertrophy in adult cardiomyocytes.4,5 Although Zou et al reported similar activation of ERK by β-AR stimulation in whole hearts, hypertrophy induced by in vivo administration of isoproterenol to transgenic mice is much more complicated than that seen in cultured myocytes because of systemic neurohumoral changes induced by β-AR and contamination by non-myocyte cells. Therefore, further investigation is needed to verify that the cross-talk discussed in cultured neonatal cardiomyocytes induced by β-AR is responsible for the hypertrophy seen in adult cardiomyocytes.

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Response

We thank Drs Shizukuda and Buttrick for their interest in our paper,1 but we disagree with some of their arguments and interpretations. Although there should be differences in various aspects between neonatal and adult cardiomyocytes, many studies have demonstrated that stimulation of β-adrenergic receptors induces activation of extracellular signal-regulated protein kinases (ERK) and hypertrophy in both cultured neonatal1-2 and adult3-4 cardiomyocytes. Communal et al5 also reported that ERK1/2 activity was increased 2.6±0.4-fold at 60 minutes by β-adrenergic receptor activation. Stimulation of β-adrenergic receptors has 2 diverse effects on both neonatal and adult cardiomyocytes: (1) induction of hypertrophy2,4 and (2) apoptosis.1,3,5 Isoproterenol (1~10 μmol/L) induces apoptosis as well as hypertrophy in neonatal1,2,3 and adult4 cardiomyocytes. Activated calcineurin may be involved in isoproterenol-induced apoptosis5 and hypertrophy4 possibly by dephosphorylating Bad and by activating NFAT-3, respectively. β-Adrenergic receptor activation might induce in vivo cardiac hypertrophy by cross-talk with many other neurohumoral factors as well as by an increase in hemodynamic overload. However, results obtained so far from cultured cardiomyocytes indicate that there is no obvious difference between neonatal and adult cardiomyocytes in terms of the effects of β-adrenergic stimulation on ERK, hypertrophy, and apoptosis.

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Through Calcineurin
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