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LKPNM: a prodrug-type ACE-inhibitory peptide derived from fish protein

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Abstract

It has been previously documented that the thermolysin-digest of ''Katsuo-bushi'', a Japanese traditional food processed from dried bonito possesses potent inhibitory activity against angiotensin I-converting enzyme (ACE). The present authors isolated eight kinds of ACE-inhibitory peptides from it. Of these isolated peptides, LKPNM (IC_{50} = 2.4 μM) was found to be hydrolyzed by ACE to produce LKP (IC_{50} = 0.32 μM) with 8-fold higher ACE-inhibitory activity relative to the parent peptide or LKPNM, suggesting that LKPNM can be regarded as a prodrug-type ACE-inhibitory peptide. For assessment of relative antihypertensive activities of LKPNM and LKP to that of captopril, they were orally administered to SHR rats to monitor time-course changes of blood pressures, whereby it was evidenced that both LKPNM and captopril showed maximal decrease of blood pressure 4 h after oral administration and their efficacies lasted until 6 h post-administration. In sharp contrast, however, maximal reduction of blood pressure occurred as early as 2 h after administration of LKP. Minimum effective doses of LKPNM, LKP and captopril were 8, 2.25 and 1.25 mg/kg, respectively. When compared on molar basis, antihypertensive activities of LKPNM and LKP accounted for 66% and 91% relative to that of captopril, respectively, whereas in vitro ACE-inhibitory activities of LKPNM and LKP were no more than 0.92% and 7.73% compared with that of captopril (IC_{50} = 0.022 μM). It is of interest to note that both of these peptides exert remarkably higher antihypertensive activities in vivo despite weaker in vitro ACE-inhibitory effects, which was ascertained by using captopril as the reference drug.

Keywords: Angiotensin I-converting enzyme inhibitor; Antihypertensive peptides; Katsuo-bushi

1. Introduction

Angiotensin I-converting enzyme (ACE) converts angiotensin I to angiotensin II known to be a strong vasopressor, besides inactivating bradykinin conducive to lowering blood pressure (Ondetti et al., 1977). Eventually, it is well known that ACE inhibitors exhibit antihypertensive activity in spontaneously hypertensive rats (SHR) or hypertensive patients (Case et al., 1978). Recently, attention has been focused on various ACE-inhibitory peptides derived from casein (Maruyama et al., 1985, 1987a,b), fish muscle (Kohama et al., 1988; Suetuna and Osajima, 1989), and other proteins (Oshima et al., 1979; Maruyama et al., 1989). Previously, we found the thermolysin-digest of dried bonito to posses potent ACE inhibitory activity, culminating in our

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