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Age and testosterone-dependent change in the expression of calcitonin-gene related peptide receptors in rat basilar arteries

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Increasing evidence has suggested that the vasoactive peptide, calcitonin gene-related peptide (CGRP), plays a pivotal role in the pathogenesis of migraine headache and counterbalancing the cerebral vasospasm due to subarachnoid hemorrhage. In this study, the impact of aging on the CGRP-induced vasodilation was investigated. Different age groups of male Sprague Dawley rats (4 weeks, 8 weeks, 16 weeks and 72 weeks old) were compared. In the rat basilar arteries precontracted with endothelin-1 (10 nM), CGRP elicited a concentration-dependent vasodilation which could be inhibited by CGRP receptor blocker α-CGRP (8-37). The maximum responses and EC_{50} values of CGRP-induced vasodilation in 4, 8 and 16 weeks old rats were not statistically different (maximum responses in the range of 86-95% relaxation and EC_{50} values in the range of 1.39-2.42 nM, $P > 0.05$). However, the maximum response and EC_{50} value of CGRP-induced vasodilation in 72 weeks old rats were 45% relaxation and 10.75 nM, respectively ($P < 0.05$, compared with 4 weeks, 8 weeks and 16 weeks old rats). It is well established that CGRP receptors are composed of calcitonin receptor-like receptors (CRLR) and receptor activity modifying protein 1 (RAMP1). As shown in Western blot, the protein levels of CRLR and RAMP1 in 72 weeks old rats were 3.2 and 3.8 times higher than in 8 weeks old rats. Since aging in male is associated with a decrease in plasma testosterone level, the effect of testosterone on CGRP response was also studied. Castration shifted the concentration-response curve of CGRP-induced vasodilation in 16 weeks-old rats to left (EC_{50} changed from 1.40 nM to 0.43 nM; $P < 0.05$) and the effect of castration could be reversed by replacement treatment with testosterone (25 mg/rat, by implantation for 4 weeks). In contrast, the maximum response of CGRP-induced vasodilation in 72 weeks old rats was significantly improved from 45% to 88% ($P < 0.05$) when the rats were treated with testosterone (25 mg/rat, by implantation for 4 weeks). The effect of testosterone in both 16 weeks and 72 weeks old rats could be inhibited by androgen receptor blocker flutamide (25 mg). Patch-clamping studies showed that the testosterone (10 nM) increased the CGRP (10 nM)-induced ATP-sensitive potassium current in human brain vascular smooth muscle cells by 2.8 times. Testosterone (10 nM) also up-regulated the protein expression levels of CRLR and RAMP1 by 3.5 and 8.7 times, respectively. The effects of testosterone on CRLR and RAMP1 expressions were inhibited by selective MAPK/ERK blockers PD98059 and U0126 (both at 10 μM). In conclusion, our results suggest that CGRP-induced dilation of cerebral arteries is impaired in aging. Testosterone exerts an age-dependent effect on CGRP-induced vasodilation. In young rats, testosterone attenuates the CGRP-induced vasodilation. However, in aged rats which are supposed to be testosterone-deficient, testosterone supplement improves the CGRP-induced vasodilation. The mechanism is not known but may be relevant to MAPK/ERK-dependent pathways which up-regulate the expression level of CGRP receptors.