Pharmacological Reports
2011, 63, 45–53
ISSN 1734-1140

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Polish Academy of Sciences

Differences between human wild-type and C23S variant 5-HT$_{2C}$ receptors in inverse agonist-induced resensitization

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Abstract:
The aim of this study was to analyze functional properties of the naturally occurring C23S variant of the human 5-HT$_{2C}$ receptor. In HEK293 cells transiently expressing the unedited forms of the variant receptor (VR) or the wild-type receptor (WTR), surface expression was determined by [^{3}H]mesulergine binding to membrane fragments. Function was examined by an aequorin luminescence-based Ca^{2+} assay. Surface expression of the VR was 116% of that of the WTR. The 5-HT-induced increase in cytosolic Ca^{2+} ($[Ca^{2+}]_i$), and its inhibition by the inverse agonist SB 206553 did not differ between VR- or WTR-expressing cells. Preexposure of VR- or WTR-expressing cells to 0.5 μM 5-HT (3 min–4.5 h) led to a practically identical time course and extent in the reduction of the 5-HT-induced increase in $[Ca^{2+}]_i$. In contrast, prolonged preexposure to the inverse agonist SB 206553 (1 μM) elevated the 5-HT-induced increase in $[Ca^{2+}]_i$ for both isoreceptors. A preexposure time of 4.5 h was necessary to significantly elevate the Ca^{2+} response of the WTR, but the VR produced this elevation within 1 h with virtually no further effect after 4.5 h of preexposure. In conclusion, prolonged preexposure to 5-HT caused equally rapid and strong desensitization of both isoreceptors. The different time course of SB 206553-induced resensitization of the two isoreceptors might be therapeutically relevant for drugs exhibiting inverse agonist properties at 5-HT$_{2C}$ receptors, such as atypical antipsychotics and certain antidepressants.

Key words:
aequorin, calcium, 5-HT$_{2C}$ receptor, C23S variant, receptor desensitization, inverse agonist, SB 206553, HEK293 cells