MOL2NET, International Conference Series on Multidisciplinary Sciences
http://sciforum.net/conference/mol2net-03

Functional characterization of α_1 adrenergic receptor in the rat locus coeruleus in vitro

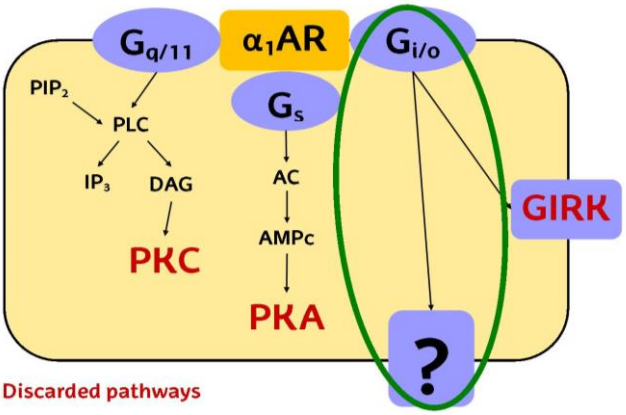
Irati Rodilla (irati.rodilla@ehu.eus)[a], Aitziber Mendiguren (aitziber.mendiguren@ehu.eus)[a] and Joseba Pineda (joseba.pineda@ehu.eus)[a]

[a] *Department of Pharmacology, Faculty of Medicine and Nursing, University of the Basque Country (UPV/EHU), E-48940 Leioa, Bizkaia, Spain*

Abstract

α_1-adrenoceptor (α_1AR) is involved in the physiopathology of the central nervous system (CNS) and could constitute a therapeutic target for neurological disorders such as drug addiction or Alzheimer´s disease. α_1AR mainly couples to $G_{q/11}$ protein, which activation leads to stimulation of phospholipase C (PLC) and subsequent activation of protein kinase C (PKC). However, other G proteins (G_i, G_s) have also been described to be coupled to α_1AR receptors. The locus coeruleus (LC), the main noradrenergic nucleus in the CNS, has been shown to express α_1AR, but to date functional role of α_1AR in the adult rat brain LC remains unclear. The aim of this study was to characterize, by single-unit extracellular recordings of LC neurons, the role of α_1AR in the regulation of the firing rate (FR) of LC neurons in adult rat brain *in vitro*. For that purpose, we first characterize the effect of the α_1/α_2AR agonist noradrenaline (NA) in the presence and absence of the α_2AR antagonist RS 79948 (0.1 µM). Then, we investigated the signalling pathway involved in the effect of NA. Perfusion with NA (100 µM) inhibited the FR of LC neurons through activation of α_2AR. However, in the presence of the α_2-adrenoceptor (α_2AR) antagonist RS 79948 (0.1 µM) perfusion with NA increased the FR of NA neurons (stimulatory effect = 114%). The stimulatory effect of NA (100 µM) was blocked by the α_1AR antagonist WB 4101 (0.5 µM). Administration of the PKC inhibitor Go 6976 (1 µM), the G protein-coupled inwardly-rectifying potassium channel (GIRK) blocker $BaCl_2$ (300 µM) or PKA inhibitor H-89 (10 µM) failed to change the stimulatory effect of NA. However, NA (100 µM) induced stimulation was reduced by 64% in the presence of the $G_{i/o}$ protein inactivator pertussis toxin (PTX) (500 ng·ml^{-1}). In conclusion, α_1AR activation stimulates the FR of NA neurons in the adult rat LC through a signalling pathway that involves activation of the $G_{i/o}$ protein. It remains to be studied the mechanism by which $G_{i/o}$ proteins stimulates the FR of LC neurons via α_1AR activation.

Graphical Abstract



References

Berridge, C.W., and Waterhouse, B.D. (2003). The locus coeruleus-noradrenergic system: Modulation of behavioral state and state-dependent cognitive processes. Brain Res. Rev. *42*: 33–84.

Ghanemi, A., and Hu, X. (2015). Elements toward novel therapeutic targeting of the adrenergic system. Neuropeptides *49*: 25–35.

Ivanov, A., and Aston-Jones, G. (1995). Extranuclear dendrites of locus coeruleus neurons: activation by glutamate and modulation of activity by alpha adrenoceptors. J. Neurophysiol. *74*: 2427–2436.

Mendiguren, A., and Pineda, J. (2007). CB1 cannabinoid receptors inhibit the glutamatergic component of KCl-evoked excitation of locus coeruleus neurons in rat brain slices. Neuropharmacology *52*: 617–625.

Osborne, P.B., Vidovic, M., Chieng, B., Hill, C.E., and Christie, M.J. (2002). Expression of mRNA and functional alpha1-adrenoceptors that suppress the GIRK conductance in adult rat locus coeruleus neurons. Br. J. Pharmacol. *135*: 226–232.

Pudovkina, O.L., and Westerink, B.H.C. (2005). Functional role of alpha1-adrenoceptors in the locus coeruleus: A microdialysis study. Brain Res. *1061*: 50–56.