β-arrestin Plays a Major Role In The Mechanism Of Action Of Antidepressant Drugs

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Abstract
β-arrestins play a pivotal role in GPCR desensitization and down-regulation. Preliminary data from our laboratory indicates that chronic treatment with antidepressant drugs (ADs) affects β-arrestin1 rat brain levels. This study concentrates on ADs mechanism of action at the post-receptor level involving 2nd messenger systems, receptor down-regulation, and regulatory elements related to receptor-G protein signalling: β-arrestin1&2, especially their interaction with MAPK cascade components. A better understanding of the involvement of β-arrestins in ADs mechanism of action might serve as a tool for (a) an optimization in therapeutic clinical use (b) designing new antidepressants through the new target for their mechanism of action (c) establishing a "gold standards" that can be used for diagnosis and monitoring response to treatment.

Hypothesis
Cellular signal transduction elements involved in receptor-G protein coupling and its regulation, play a pivotal role in the biochemical mechanism of action of antidepressant drugs.

Research Objectives
To study the mechanism of action of antidepressants at the post-receptor level involving regulatory elements related to GPCR desensitization process: β-arrestin1/2 and ERK1/2.

Materials & Methods

Experimental model: C57 rat glialoma cells treated acute or chronically with various classes of antidepressants in the presence or absence of the MEKI1/2 inhibitor - U0126.

CAMP measurement: radioligand assay.

Receptors down-regulation: radioligand binding assay with the hydrophilic radioligand (3H)GSP-12177.

Proteins function and levels: confocal microscopy and western blotting.

Results

I. cAMP measurement

Results cont.

II. Receptors down-regulation

Fig 2: cAMP levels after acute treatment (20, 45, 90 min) with 50 nM imipramine in the presence or absence of 50 μM imipramine. cAMP values are mean ± SD of at least 3 independent experiments.

- No significant difference between the chronic and the acute treatment.

- Binding levels of [3H]GSP-12177 were not decreased after chronic treatment with the different classes of drugs.

- Inhibition of ERK2/2 activity caused a significant decrease in β-arrestin2 levels in both ADs treated and untreated cells.

- Inhibition of ERK2/2 activity caused a significant increase in β-arrestin2 levels only in ADs treated cells.

Conclusions

- Drugs effects on cAMP level were found to be irrelevant to ADs therapeutic mechanism of action.

- The delayed mechanism of action of ADs does not directly involve down-regulation of receptors.

- The present data supports the involvement of β-arrestin1&2 and ERK1/2 in the mechanism of action of ADs.

- Suggested theory: prior to ADs treatment β-arrestin2 acts as a cytosolic scaffold for activated ERK hence reducing ERK-dependent transcription, and presumably β-arrestin1 transcription. By reducing β-arrestin2 levels ADs enable activated ERK2/2 translocation to the nucleus, thus increasing β-arrestin1 levels.

- The results also support the possibility that ADs can induce transcription of β-arrestin2 by a non-ERK2/2 dependent pathway.

- The described findings also indicate that β-arrestins may serve as diagnostic markers for major depression.

References