Journal of Hepatology and GastrointestinalDisorders
ISSN2475-3181
2021
Vol.7 No.2

Progesterone and selective ligands of membrane progesterone receptors increase apoptosis in human pancreatic adenocarcinoma cells BxPC3 via p38 MAPK activation.

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Abstract

Progesterone (P4) regulates the women reproductive functions by acting primarily through nuclear receptors (nPRs). However, its functions are not limited to the reproductive sphere. In 2003 membrane progesterone receptors (mPRs) were identified. We recently discovered selective ligands of these receptors: 19-hydroxypregn-4-en-20-one (I) and 19- hydroxy-5β-pregn-3-en-20-one (II) that do not interact with nPRs. Maximal level of mPRs expression was found in BxPC3 human pancreatic adenocarcinoma cells lacking of nPRs.

Aim of Research: The aim of this work was to evaluate the effects of P4 and mPRs selective ligands (I) and (II) on apoptosis of BxPC3 cells and to identify the mediators of their action.

Method: Activation of p38 MAPK and JNK by different concentrations of steroids was analyzed by Western blotting with antibodies against phosphorylated forms of these protein kinases. The levels of DNA fragmentation in BxPC3 cells in the absence or presence of p38 MAPK and JNK inhibitors were measured by TUNEL assay with following flow cytometry analysis.
Data were analyzed using GrapgPad Prism 6 software. For the comparative analysis ordinary one-way ANOVA Kruskal-Wallis test was performed. Statistical significance was considered for a p value < 0, 05.

Fig.1: Example of P4 action on phosphorylated form of p38 MAPK and JNK. Left to right: control, P4 (1mkM), P4 (5mkM), P4 (20mkM).

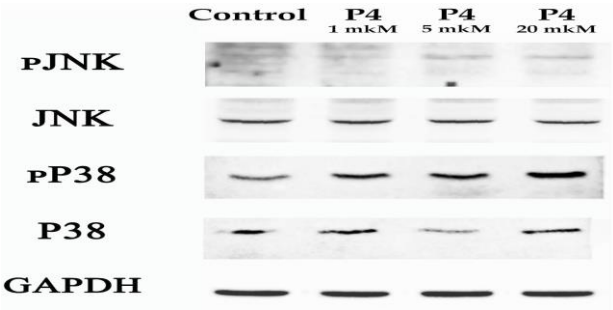


Fig.2: Action of P4 and compound (I) and (II) on DNA fragmentation in BxPC3 cells.

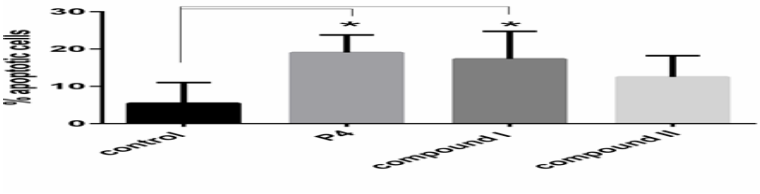
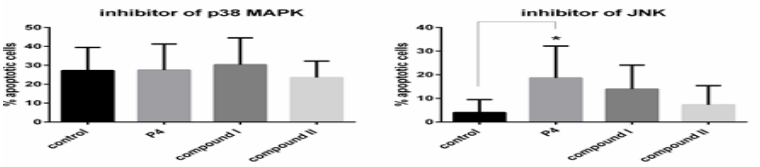


Fig.3: Action of P4 and compound (I) and (II) on DNA fragmentation in BxPC3 cells in the presence of p38 MAPK inhibitor and JNK inhibitor.



Results: P4 and selective ligands of mPRs (I) and (II) were found to increase p38 MAPK and JNK phosphorylation in dose-dependent manner (fig1).The levels of DNA fragmentation in BxPC3 cells were shown to increase by action of P4 and compound (I) 3.5-fold and 3.2-fold respectively and by compound (II) - 2.3-fold (fig2). These effects were completely abolished in the presence of p38 MAPK inhibitor and weakened in the presence of JNK inhibitor (fig3).

Conclusion: p38 MAPK plays a key role in mediating the enhancement of pancreatic adenocarcinoma cells apoptosis by P4 and selective mPRs ligands (I) and (II). The reported study was funded by RFBR, project number 20-015-00092

Bibliography

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19th Euro-Global Gastroenterology Conference; March 19,2021.

Abstract Citation:

Gorchakov, "Progesterone and selective ligands of membrane progesterone receptors increase apoptosis in human pancreatic adenocarcinoma cells BxPC3 via p38 MAPK activation." Gastro Conference 2021, 19thEuro-Global Gastroenterology Conference- April 19, 2021