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Review

Rapid estrogen actions on ion channels: A survey in search for mechanisms

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ABSTRACT

A survey of nearly two hundred reports shows that rapid estrogenic actions can be detected across a range of kinds of estrogens, a range of doses, on a wide range of tissue, cell and ion channel types. Striking is the fact that preparations of estrogenic agents that do not permeate the cell membrane almost always mimic the actions of the estrogenic agents that do permeate the membrane. All kinds of estrogens, ranging from natural ones, through receptor modulators, endocrine disruptors, phytoestrogens, agonists, and antagonists to novel G-1 and STX, have been reported to be effective. For actions on specific types of ion channels, the possibility of opposing actions, in different cases, is the rule, not the exception. With this variety there is no single, specific action mechanism for estrogens *per se*, although in some cases estrogens can act directly or via some signaling pathways to affect ion channels. We infer that estrogens can bind a large number of substrates/receptors at the membrane surface. As against the variety of subsequent routes of action, this initial step of the estrogen's binding action is the key.

Contents

Abbreviations: $[Ca^{++}]_i$, intracellular Ca^{2+} concentration; 2ME2, 2-methoxyestradiol, a natural metabolite of estradiol; 4-OH-Tmx, 4-hydroxytamoxifen, a metabolite of Tmx; 5-HT_3R, 5-hydroxytryptamine receptor subtype 3; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; BBP, butyl benzyl phthalate, a plasticizer and an environmental pollutant, exerts genomic estrogenic-like effects via estrogen receptors; BK or Maxi-K or slo-1, big conductance Ca^{2+}- and voltage-activated K^+ channel; BPA, bisphenol A; BPA-Ms, BPA monosulfate, membrane-impermeable; Ca-L, L-type Ca^{2+} channel; cAMP, cyclic adenosine monophosphate; Ca-N, N-type Ca^{2+} channel; Ca-T, T-type Ca^{2+} channel; Cav, voltage-gated Ca^{2+} channel; cGMP, cyclic guanosine monophosphate; CREB, cAMP response element-binding protein; DES, diethylstilbestrol, an endocrine disruptor; DPN, diarylpropionitrile, ERβ agonist; DTP, diethyl terephthalate, has estrogenic actions; E2, 17β-estradiol; EB, 17β-estradiol benzoate; E-BSA, E2 covalently linked to membrane impermeable BSA (bovine serum albumin); E-BSA-FITC, E-BSA conjugated to fluorescein isothiocyanate; EBT, ethylbromide Tmx, impermeable; Edrp, endocrine disruptor; EE2, ethynylestradiol a derivative of E2; E-HRP, E2 conjugated to horseradish peroxidase; ERK1/2, extracellular signal-regulated kinase 1/2; ERβ1, the long form estrogen receptor subtype β; $GABA_A$R, γ-aminobutyric acid receptor subtype A; GIRK, G protein-coupled inwardly-rectifying potassium channels; hERG, human ether-à-go-go-related gene encoded K^+ channel; IsK, slowly activating, voltage-depend K^+ current; K_A, transient A-type K^+ channels; KAR, kainate-gated receptor/channel; K_{ATP}, ATP-sensitive K^+ channel; KCNQ1, voltage-gated K^+ channel subfamily KQT member 1; Kdr (or Kr), delayed rectifier K^+ channel; Kir, inward rectifier K^+ channel; Kv, voltage-gated K^+ channel; MAPK, mitogen-activated protein kinases; nAChR, nicotinic acetylcholine receptor; NMDAR, N-methyl-D-aspartate receptor; NO, nitric oxide; $P2X_3$, P2X purinoceptor 3 channel; phytoE, phytoestrogen; PIP_2, phosphatidylinositol 4,5-bisphosphate or PtdIns(4-5)P_2; PKA, protein kinase A; PKC, protein kinase C; PKG, protein kinase G; PLC, phospholipase C; PPT, propylpyrazoletriol, erα agonist; SERM, Selective Estrogen Receptor Modulator; STX, diphenylacrylamide compound (does not bind to classical estrogen receptors); Tmx, tamaxifen; TPE, triphenylethylene, a SERM; XE, xenoestrogen.

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1. Introduction

The very existence of rapid estrogenic actions is, by now, well established beyond question. Hereafter we will refer to these simply as 'rapid actions' or 'rapid effects'. It is difficult to conceptualize these actions because they are wildly diversified, starting from the estrogen receptors involved all the way through the diversity of the tissues and cells they affect. Their effects on ion channels offer no exception to this diversity.

There are very few review articles on this subject, and those focus on certain type of channels. The mechanism of one kind of estrogenic agent on a single type of ion channel may be figured out. But this does not help the understanding of the rapid actions as a whole, because the mechanism found in one particular case may not be applied to others. In view of this, we hope to cover as completely as possible the ion channels investigated for rapid estrogenic actions.

2. The analyses of the reported results

In this review, we use a simple, straightforward method in the attempt to cover mechanisms of rapid actions. We searched the literature for relevant articles and list the important characteristics, such as the type of estrogen and dose use, the type of channel studied, etc., from each article's content in Excel spread sheets. We then used the Sort function to cross-reference different kinds of characteristics to evaluate the possibility of an existing mechanism. Since many reports used multiple kinds of estrogens on multiple types of ion channels, therefore the basis of incidence of occurrence is 'a case' rather an article or report. A case is defined as one kind of estrogenic agent acting on a certain subtype of channel. Hence, a report/article may have many cases; or the number of references cited for a particular incidence may be less than the number of incidences mentioned.

3. Estrogenic agents employed

As expected, 17β-estradiol (E2) is the most frequently (171/276 cases) employed, followed by Selective Estrogen Receptor Modulator (SERM) (61/276) and endocrine disruptors (10/276). More interesting is the comparison of permeable and impermeable versions of the same estrogenic agent. As presented in Table 1, in all but one case, impermeable agents mimicked their permeable version or worked by themselves. This result confirms the well accepted concept that rapid actions are mediated by site(s) of receptors on the outside of the cells.

Table 1
Results showing membrane-impermeable form of estrogens are as effective as their permeable versions.

Number of cases	Agent*	Effects	Ion channel	References
26	E2 = E-BSA (18); E2 = E-HRP (2); E2 = E-peroxidase (1); Tmx = EBT (2); Estrone = estrone oximes (1); Estrone = Quat DME-estradil (1); BPA = BPA-Ms (1).	↑ (16); ↓ (10).	Ca (12); K (10); Na (1); Ligand-gated (3).	[9–33]
2	E-BSA; E-BSA-FITC	↑ (2)	Ca-L	[34,35]
1	E2≠E-BSA	↓	Kv2	[36]

* In this and all other tables, equal sign, "=", similar in action; number in parentheses indicate the number of cases.

4. Ion channels investigated

The type/subtypes of ion channels investigated are listed in Table 2. Potassium channels are the most popular, followed by calcium, ligand-gated, sodium and lastly chloride channels. Important and interesting in this table is the lack of consistency of estrogen effects on most types of channels. For example, estrogens could exert stimulatory (↑, increase channel activity, activate or open channels) and inhibitory (↓, decrease, block or abolish channel activity, or channel's open probability) effects on BK (big conductance Ca^{2+}- and voltage-activated K^+ channels) and Ca-L (L-type Ca^{2+} channels), the two most investigated channels, and others. These diversity and often conflicting results are very difficult to be reconciled with the idea of a unified mechanism for rapid actions.

5. Search for causes/explanations for the conflicting rapid effects on BK and Ca-L

In attempts to find out possible explanations for these diverse and conflicting results, we focused on BK and Ca-L and made some detailed analyses. These two types of channels were chosen not only because they are the most intensively investigated but also because of a basic almost all difference – BK is more often "stimulated" by estrogens than Ca-L. The results of these analyses are presented in Table 3. First, we looked at the kinds of estrogenic agents used. The agents that caused ↑ as well as ↓, are Bold-faced. One can see almost all kinds of agents that caused ↓ also caused ↑ in BK. Similarly, all those that caused ↑ in Ca-L also induced ↓. Obviously, the conflicts are not due the estrogens used.

We then looked at doses of estrogens used. For BK, the doses that induced either type of response markedly overlapped. Hence the doses used cannot account for the opposite responses of BK channels to estrogens. The situation is different for Ca-L channels. Here ↑ responses were induced by low doses ranging from pM to nM, whereas ↓ responses were induced by higher μM doses in all but one case. Thus, for Ca-L channels, the difference in estrogen doses can be a cause for the opposite responses.

The signaling pathways involved were also examined. Unfortunately, the number of cases that investigated these pathways are too few to allow for making firm conclusions. Still, looking for potential clues, we turned to the tissue/cells used. For the BK channel, the weighted proportion of muscle (and, even fewer, neuronal cases) may together account for the occurrence of more ↑ responses. The situation is just the opposite for Ca-L channels, where the weighted muscle proportion is associated with ↓ responses. Thus, the response of an ion channel to rapid estrogenic action does not appear to be dependent on the kind of estrogen agents, but may be affected by the dose and/or the preparation employed.

6. Direct rapid estrogen actions on ion channels

The direct action is one of the most attractive mechanisms proposed for rapid actions. It states that estrogens act by binding directly on parts of ion channels. It was based mostly on precise single-channel recordings (mostly from excised inside-out patches, see references in Table 4), but also on other methods, such as binding studies [1–3], site mutations [4], pharmacological and biophysical analysis [5], kinetics of estrogen effects [6], etc. Results from such studies are presented in Table 4. From the list of estrogen used it appears almost all kinds of estrogenic agents can act directly on ion channels, with a possible exception of G-1. When effective, the direct actions of estrogens are divided about evenly in either direction on the channels, except for BK. Close