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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.

Keywords

BK; estrogen binding; ion channel kinetics; L-type Ca^{2+} channel; Selective Estrogen Receptor Modulator (SERM); signaling pathway

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,

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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.

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.

Estrogenic agents employed

As expected, 17 β -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.

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 ($\uparrow$, increase channel activity, activate or open channels) and inhibitory ($\downarrow$, decrease, block or abolish channel activity, or channel's open probability) effects on BK (big conductance Ca²⁺- and voltage-activated K⁺ channels) and Ca-L (L-type Ca²⁺ 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.

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 $\uparrow$ as well as $\downarrow$, are Bold-faced. One can see almost all kinds of agents that caused $\downarrow$ also caused $\uparrow$ in BK. Similarly, all those that caused $\uparrow$ in Ca-L also induced $\downarrow$. 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 $\uparrow$ responses were induced by low doses ranging from pM to nM , whereas $\downarrow$ 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 $\uparrow$ responses. The situation is just the opposite for Ca-L channels, where the weighted muscle proportion is associated with $\downarrow$ 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.

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 examination of the results of the three inhibitory cases raised the possibilities that: 1) the E2 metabolite, 2ME2, might act on a “negative” site(s) on BK where other estrogens won't bind; and/or 2) the BKs on endothelial cells are different (perhaps structurally or perhaps by subtype unit) from BKs in other tissue/cells. Of course these possibilities remain to be further evaluated.

Many of the studies on direct actions used high doses of estrogens, in μM ranges, especially when working on muscle preparations. This does not, however, discredit these observations because such studies were usually conducted on stripped down preparations, such as excised, cell-free patches or even artificial bilayers accompanied by no or very little cytoplasm. The reason for using high doses could be that estrogens may also act on something else to work synergistically with the direct actions. As will be further discussed later, rapid activation of signaling systems would be a good candidate for this.

Another interesting result is the lack of direct rapid action in three cases. The lack of an effect on the BK [7] is a big surprise in view of the twenty one positive cases. The one possible reason we could find is that in this particular case G-1, the GPER agonist, was used. Is it possible that G-1 binds only to G-protein coupled receptors? It would be interesting to check out whether G-1 can bind to BK or to other ion channel.

Two of the negative cases come from the same paper [8]. It reported that E2 had no effect on the two glutamate's ligand-gated channels, NMDA or KAR. As far as we can see, this is the only single-channel recording study on these two channels. Since both types of ligand-gated channels are affected by estrogens (see Table 2 and 5), these negative results indicate that the direct action, solidly demonstrated when positive, is not the only mechanism underlying rapid estrogen action.

Rapid estrogen actions via signaling pathways/systems

There are many studies using agonists or, more often, inhibitors to activate or block certain signaling pathways and subsequently observe the effect on rapid estrogen actions. The results of the studies available are listed in Table 5. There are a few things that are obvious. **First**, a wide variety of signaling systems are involved in mediating rapid estrogen actions. **Second**, a wide variety of estrogenic agents are effective. They include E2, SERMs, endocrine disruptors, phytoestrogens, ER agonists, the G-1 that did not have direct action, and the novel STX. **Third**, unlike works on direct actions, studies shown in Table 5 generally use estrogen doses in nM. This may indicate that rapid actions mediated by signaling systems are more sensitive to estrogens. However, since this kind of investigation is usually done with intact cells, estrogens might activate more than one type of rapid actions, e.g., both direct action and signaling path mediated (see more discussion about this below). **Fourth**, a wide variety of type and subtype of ion channels are affected by rapid actions, including NMDAR and KAR that were not susceptible to direct action (see Table 4). **Fifth**, the effects of estrogen action are, as usual, pretty evenly stimulatory and inhibitory. We could not find any association between the effects with estrogen types, doses or types of ion channels.

The actual scope of rapid actions via signaling pathways may be wider than that shown in Table 5, because investigators usually attempted to look at the specific pathway they are interested in and only if they already suspected that the pathway was involved.

The origin of the wide-spread rapid action diversity

The most important of our literature survey is the finding that almost all using impermeable estrogens found them effective as permeable ones. This is important because it implies that rapid actions are induced by estrogens working outside the cell. They don't have to, and probably do not, get inside the cell to bind and activate second messengers. Therefore, we can safely assume that the majority, if not all, of rapid actions are originated at estrogen binding sites at membrane's extracellular surface. When substrate is bound, it could trigger a build-in action specific to this substrate. Since estrogens are promiscuous in binding, as indicated by the wide range of estrogens that are effective and the continuous finding of new

membrane receptors for them, it is no wonder that rapid estrogen actions are so diverse. Thus, the initial step, the binding of estrogens to membrane substrates, dictate the ensuing estrogen action and the promiscuous binding is the origin of the diversity rapid actions. Hence, this initial step is the key to the understanding of rapid estrogen actions.

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Abbreviations

[Ca⁺⁺]_i

intracellular Ca²⁺ concentration

2ME2

2-Methoxyestradiol, a natural metabolite of estradiol

4-OH-Tmx

4-Hydroxytamoxifen, a metabolite of Tmx

5-HT₃R

5-hydroxytryptamine receptor subtype 3

AMPA

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 Ca²⁺- and voltage-activated K⁺ channel

BPA

Bisphenol A

BPA-Ms

BPA monosulfate, membrane-impermeable

Ca-L

L-type Ca²⁺ channel

cAMP

cyclic adenosine monophosphate

Ca-N

N-type Ca²⁺ 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, $\text{ER}\beta$ 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

 $\text{ER}\beta 1$

the long form estrogen receptor subtype β

GABA_AR

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

P2X₃

P2X purinoceptor 3 channel

phytoE

phytoestrogen

PIP₂

phosphatidylinositol 4,5-bisphosphate or PtdIns(4,5)P₂

PKA

protein kinase A

PKC

protein kinase C

PKG

protein kinase G

PLC

phospholipase C

PPT

propylpyrazoletriol, ER α agonist

SERM

selective estrogen receptor modulator

STX

diphenylacrylamide compound (does not bind to classical estrogen receptors)

Tmx

tamoxifen

TPE

triphenylethylene, a SERM

XE

xenoestrogen

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-estradiol (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	[33, 34]
1	E2 E-BSA	↓	Kv2	[35]

* equal sign, "=", similar in action; number in parentheses indicate the number of cases.

Table 2

Ion channels investigated.

Ion Channels		Effects and numbers of rapid estrogen actions					References ^b
Type	Subtype	↑ <i>q</i>	↓	--	others	Total	
K ⁺	BK	35	12	2	1	50	[3, 7, 16, 17, 24, 29, 32, 36-56] // [1, 13, 44, 57-62] // [63, 64] // [65].
	Kdr (or Kr)	1	13	1	0	15	[19, 35, 66-76].
	KATP	7	8	0	0	15	[28, 77-89].
	Kir	1	10	2	0	13	[66, 71, 73, 74, 90-97].
	K _A	0	7	3	0	10	[63, 68, 73, 74, 76, 91, 98-100]
	GIRK	0	6	0	0	6	[101-105]
	K _v	0	2	2	0	4	[9, 32, 35]
	hERG	0	4	0	0	4	[106-109]
	KCNQ1	0	4	0	0	4	[107, 108, 110, 111]
	Misc	6	6	2	0	14	[6, 57, 58, 91, 97, 112-118].
Ca ²⁺	Total	50	72	12	1	135	
	Ca-L	7	28	2	0	37	[12, 21, 34, 119-122]/[6, 14, 22, 63, 66, 123-141]/[51, 88].
	T-type	0	4	1	0	5	[6, 141, 142] // [22]
	N-type	1	2	0	0	3	[143] // [22, 126].
	Cav	1	8	0	0	9	[5, 61, 84, 144-149].
	[Ca ²⁺] _i	11	6	1	0	18	[10, 11, 18, 30, 33, 86, 114, 150-153] // [15, 28, 148, 154-156] // [157]
	Ca ²⁺ influx	6	3	0	0	9	[23, 158-162] // [26, 163, 164].
	Misc	4	6	0	0	10	[2, 84, 165-168] // [72, 169, 170].
	Total	30	57	4	0	91	
	All	2	10	0	0	12	[75, 171] // [31, 66, 68, 73, 97, 107, 108, 172, 173].
Na ⁺	All	2	5	1	0	8	[174, 175] // [66, 111, 176-178] // [66].
Cl ⁻	KAR	3	0	1	0	4	[8, 179-181].
Ligand-gated	nAChR	1	4	0	0	5	[4, 182-184].
	NMDAR	4	0	2	0	6	[8, 25, 144, 185-187].
	5-HT ₃ R	0	2	0	0	2	[172, 182]

Ion Channels		Effects and numbers of rapid estrogen actions					References ^b
Type	Subtype	↑ ^a	↓	--	others	Total	
	AMPA	1	0	0	0	1	[181]
	P2X3	0	2	0	0	2	[188, 189].
	GABA _A R	0	1	0	2	3	[190, 191]
	Total	9	9	3	2	23	

^a symbols: ↑, denote increase, activation; ↓, reduction, inhibition, blockade; --, no significant effect; others, undefined modulation.

^b References for different effects are presented in order in different clusters separated by //.

Table 3

Analyses of the conflicting results from BK and Ca-L.

Ion channel	Estrogen action	Cases n=	Estrogens		Signaling path	Tissue/cell used (n, %)	Ref's
			Agent	Dose			
BK	↑	35	E2; n=18; E2=Tmx, n=2; E2=PhytoE, n=2; phytoE, n=3; BPA, n=2; Tmx, n=7; G-1, ICI 182,780, estrone, DPN, ppt, n=1 each; E2=E-BSA, n=2; Tmx=imper, n=2; BPA=BPA-Ms, n=1;	100 nM to 100 mM	cGMP, n=5; cAMP/PKA, n=1	Muscle (23, 66%); Neuron (1, 3%); HEK-293 (3,8%); MCF-7 (2, 6%); Others (6, 17%).	[3, 7, 16, 17, 24, 29, 32, 36-56].
	↓	12	E2, n=7; E2 metab, n=2; ICI 182,780, n=1; Tmx, n=2; E2=E-BSA, n=1; Tmx=imper, n=2;	100 pM to 30 mM	PKA/PKC, n=1	Muscle (3, 25%); Neuron (4, 33%); HEK-293 (2, 17%); Endothelial cells (3, 25%).	[1, 13, 57-62, 192].
Ca-L	↑	7	E2, n=5; E-BSA, XE, n=1, each; E2=E-BSA, n=1; E2=E-peroxidase, n=1.	1 pM to 100 nM	cAMP/PKC, n=1.	Muscle, n=2 (29%); Neuron, n=1 (14%); Others, n=4 (57%).	[12, 21, 34, 119-122]
	↓	27	E2, n=19; EB, EE2, DES, XE, phytoE, ICI 172,780, n=1, each; SERM, n=2; E2=E-BSA, n=2; E2=DES=EE2, n=2; E2=ICI 172,780, n=1.	1-100 mM *	PLC-MAPK-CREB, n=1; G-protein, n=1.	Muscle (16, 59%); Neuron (9, 33%); Others (2, 8%).	[6, 14, 22, 63, 66, 123-137, 139-141].

* except for one study that used 1-100 pM.

Table 4

Results of experiments designed to investigate the possibility of estrogens acting/binding directly to ion channels.

Methods	Number of cases	Estrogenic agents	Doses	Ion channels	Effects	References
Single-channel recording of BK	21	E2 (10); ICI 182780 (2); 2ME2 (2); DPN E2 (2); BPA (1); BPA=BPA-Ms (1); Tmx (5); 4-OH Tmx (1); EBT (1); PPT+DPN (1).	mM (11); nM (7).	BK (21)	↑(18); ↓ (3).	[1, 3, 9-27].
Single-channel recording	4	E2 (2); 2ME2; Tmx.	mM (4)	[Ca ²⁺] _i ; K; Slack (2); Cl ⁻	↑ (2); ↓ (2).	[11, 28-30].
Single-channel recording	3	E2 (2); G-1.	100 nM (G-1)	BK; NMDA; KAR.	-- (3)	[7, 8]
Single-channel recording and others	2	ERb1 5-20 nM; Tmx >10 mM	5-20 nM; >10 mM.	Ca-RyR; Cl ⁻	↑ (1); ↓ (1).	[2, 31]
Other than single-channel recording	7	E2 (3); Tmx, EBT; BPA; DES=EE2=E2	mM (5)	5-HT ₃ ; Kdr; Ca-L; Cav; nAChR	↑ (2); ↓ (4).	[4-6, 32-34].

Table 5

Rapid estrogen actions involving signaling systems.

Signalling system involved	Number of cases	Estrogenic agents	Doses	Ion channels	Effects	Ref's
cGMP-PKG-NO	11	E2 (10); Tmx (1); ginsenoside Re (2); E2=E-HRP (2); E2=DES=BPA (1)	all in nM	[Ca ²⁺] _i (3); BK (5); KATP (3); Ca ²⁺ oscillation (1); Ks (1).	↑ (7); ↓ (7).	[28, 39, 49, 52, 56, 67, 86, 154, 155].
MAPK-ERK1/2-CREB	7	E2 (3); E2=E-BSA (1); E-BSA-TTTC (1); E2=G-1=PPT (1); ICI 182780 (1)	10 to 100 nM	Ca-L (3); [Ca ²⁺] _i (1); BK (1); P2X3 (1); ASIC (1).	↑ (4); ↓ (2); other (1).	[33, 65, 120, 123, 166, 189, 193].
cAMP	7	E2 (4); E2=G-1=PPT (1); E-BSA (1); DES (1).	10 pM to 100 nM	Ca: Ca-L, Cav; K: BK, KATP, K; Ligand-gated: AMPA/KAR, P2X3.	↑ (5); ↓ (2).	[34, 53, 82, 113, 160, 181, 189].
G-proteins; G-proteins/PLC	8	E2 (3); E2=E-BSA (5); E2=E-BSA=S-TX (1)	nM (5); mM (3).	Ca: Ca-L, Ca-T, Cav, [Ca ²⁺] _i ; K: K, Kir; Ligand-gated: KAR.	↑ (4); ↓ (4).	[18, 22, 23, 96, 113, 146, 161, 179].
PIP2	3	Tmx (1); Tmx=4OH Tmx=Raloxifen (1); Tmx=4OH Tmx (1).	nM to mM.	Kir (1); KATP (1); GIRK (1).	↓ (3)	[94, 105]
PKA	5	E2 (3); E2=G-1 (1); E2=G-1=PPT (1).	10-100 nM	BK (1); [Ca ²⁺] _i (1); AMPA/KAR (1); P2X3 (1); Nav (1).	↑ (4); ↓ (1).	[53, 166, 171, 181, 189].
PKC	4	E2 (3); E2=E-BSA (1);	1-100 nM	Ca (1); [Ca ²⁺] _i (2); Cl (1).	↑ (3); ↓ (1).	[18, 166, 167, 176].
PKA and PKC	9	E2 (6); E2=E-BSA (2); BPA (1).	nM (5); mM (2).	[Ca ²⁺] _i (3); Ca HVA (1); KATP (1); KCNQ1 (1); GIRK (1); Na (2).	↑ (4); ↓ (4); other (1).	[18, 31, 89, 101, 111, 149, 150, 166, 173].
Misc	5	E2 (1); E2=E-BSA (3); CEE (1).	nM (2); mM (1).	[Ca ²⁺] _i (1); Cav (1); NMDA (2).	↑ (3); ↓ (2).	[11, 19, 25, 145, 186].