

Ray Peat's Newsletter

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Estrogen Receptors--what do they explain?

In the last couple of years, hundreds of people have asked me about estrogen receptors: "What does it mean that a tumor has, or doesn't have, estrogen receptors?" "What does progesterone do to estrogen receptors?" "What do weak estrogens or phytoestrogens do to the estrogen receptors?"

There are two main situations in which physicians are telling people about "estrogen receptors." Tumor cells are said to be "estrogen-receptor negative" or "estrogen-receptor positive," usually based on the reaction of artificially prepared antibodies with samples of the tissue. It is considered a good sign when the cells are "receptor

In engineering, a "transducer" is a device for transmitting energy from one system to another, converting it appropriately, for example, turning pressure into electrical voltage, or turning an electrical signal into a light signal. In biology, the word is often used to describe the problem of understanding how sensory nerves are able to convert, for example, a photon of light into a nervous impulse in the retina or optic nerve. We are always "transducing" our environment into experience. Our experience is "transduced" into anatomy, structural responses that occur with learning and development...

positive," because that means that they resemble normal tissue. Some physicians also talk about the estrogen receptors, in a more generalized way, in relation to their dietary recommendations or in relation to the use of supplementary estrogen or progesterone.

In the case of the laboratory results that show a tumor to be "estrogen-receptor positive," it is important to remember that the presence of this type of protein is a normal tissue property--even the normal eye's retina is "estrogen-receptor positive." Breast tissues, including tumors, also normally contain "receptors" for vitamin A, thyroid hormone, progesterone, oxytocin (a pitui-

If a city is being evacuated, its railroad transportation system will be quickly "saturated," and the impatience of a million people waiting for a ride won't make much difference. But if they decide to leave on foot, by bicycle, boat, or balloon, in all directions, they can leave as soon as they want to, any number of people can leave at approximately the same time. A "specific" system is "saturable," a "nonspecific" system isn't saturable. The idea of a cellular "receptor" is essentially that of a "specific" transport and/or response system. Specific transporters or receptors have been proposed for almost everything in biology—for very interesting ideological reasons—and the result has been that the nonspecific processes are ignored or suppressed. Mistaken ideas about cholesterol, vitamin C, adrenalin, sodium, light, estrogen, etc., have been promulgated and accepted, becoming standard text-book doctrine, because of those ideological commitments.

tary hormone), and for a great number of other hormones and growth-regulating factors. The absence of the "estrogen-receptor" is just one indication that the tissue is abnormal. Better clues to the cancerous nature of a breast tumor might be found in the presence of the "heat-shock proteins" or even the "prostate specific antigen," rather than in the "estrogen receptor," but the protein (or, rather, group of proteins) called "the estrogen receptor" has been of interest to oncologists partly because of the fact that estrogen is involved in the development of cancer, and because estrogens and

antiestrogens have been used to treat breast cancers.

As long as it is recognized that its presence or absence in a tumor is just one indication of the tissue's normality or abnormality, using it to characterize a tumor needn't cause any problems.

But some people are using the term, or the concept, in potentially dangerous ways, so it is very important to see what is going on, and whether the "estrogen receptor" is anything people should even be talking about.

Tamoxifen, an "antiestrogen," competes with ordinary estrogens for binding sites on the "estrogen receptor" (though it has other actions), and its value in protecting breast tissue against estrogen's effects is recognized. However, it causes uterine cancer, and is also toxic to the liver and other tissues. The drug companies would like to have drugs that oppose estrogen's cancer-causing effects, without the toxicity of tamoxifen.

The drug companies are creating a culture in which the special properties of the "estrogen receptors" are to be the defining features for the special properties of the new "designer" estrogens and antiestrogens, the "Selective Estrogen Receptor Modulators" (SERMs), which will allow the new drugs to be approved solely on the basis of their effects on the estrogen receptors, which apparently are clear and simple molecular interactions, without reference to their actual effects on the health of patients.

This is closely analogous to the present situation in which estrogen is claimed to prevent heart disease, on the basis of its effects on certain "markers" of heart disease. The substitution of "markers" for the realities of sickness and therapeutic outcome has been one of the drug industry's cleverest achievements. It allows them to sell "HIV-antiviral" drugs for people who aren't sick and who might not even have the virus, on the basis that they--or their mother--have antibodies which could indicate that they have been exposed to the virus.

The claim will be made that the newer SERMs (e.g., raloxifene) are better than tamoxifen, because they don't activate the estrogen receptors in the uterus, and so shouldn't cause uterine cancer, as

tamoxifen does. This will allow them to be sold to patients who are told that they "need estrogen," as well as to the patients who will be told that they need "an antiestrogen." If the drugs aren't tested properly, it might be generations before all the side effects are discovered, and their damage to public health could be greater than all of the pharmaceutical debacles that have already occurred.

In the 1950s and 1960s, the ability of bacteria to adapt to changes in their food supply was explained in terms of a simplified feedback system. In bacteria, specific proteins were found to regulate genes in response to the type of food available, but even in that simple organism, that theoretical model is inadequate and misleading; the favorite gene of the people who insisted on the orthodox regulator model, actually undergoes adaptive mutation, which was exactly what their model was supposed to explain away (J. Cairns and P. Foster, *Genetics* 128(4), 695-7-1, 1991). This oversimplified idea was taken as a model for explaining how complex organisms respond to hormones, such as estrogen. It was the prestige of molecular biology, and the "classical simplicity" of the genetic model, that made the idea persist, even when there were many reasons for believing that it was entirely inappropriate as a model for mammalian or human physiology.

The idea of the estrogen receptor has been around for 40 years, but it's only in the last few years that the candidate-protein has been studied with real clarity. For its first 15 or 20 years, the status of the "estrogen receptor" was just hypothetical-philosophical, and that mystique is even more powerful now, adding a quasi-religious significance to the few facts that have been produced. **For that reason, we can't understand the full meaning of the "estrogen receptor" until we know why so many people were so sure that "it existed."**

In the 18th century, varieties of platonism (the philosophies that make up Rationalism) were popular among the Tories, because the doctrine allowed them to believe that they were endowed at birth with innate knowledge of what is true and

good, and that things were always going to be essentially as they were, without the need for special effort by them. John Locke proposed that people are born without any knowledge (a philosophy of experience or empiricism), and so everyone, through effort and opportunity, can learn. Political upstarts, including the American colonists, preferred this idea, because it indicated that change is possible. Already in the 18th century, people like Erasmus Darwin were suggesting that nature *progressed*, learning even to make new species, while the conservative opposition held that although some species might have become extinct, new species could never appear. Lamarck, Buffon, and Erasmus Darwin believed that organisms learned from experience, and through experience, adapted themselves to their changing environment, but the orthodox biologists held that the identities of plants and animals were inherited and unchanging--nature had to fit the Tory Rationalist philosophy.

After the American and French revolutions, scientists in the different countries often found it convenient to compromise between absolutely rigid Rationalism and excessively flexible Empiricism, and they found a rationale in some of the ideas of Kant, who had made sort of a fusion of Rationalism with Empiricism, admitting that we do learn through our senses, but that what we learn in that way is superficial, that we can never know the "things in themselves." About the things in themselves, we can guess, and our guesses will be limited by our own rational limits. The neokantians came to see the correspondence between our "inner rational nature" and the "unknowable things in themselves" in terms of mathematical forms. We could work out the possible mathematical forms in our minds, and then through the little peep-holes of our senses, we could do experiments to check whether the "things in themselves" were obeying one mathematical "law" or another. Karl Popper's writings in the 20th century clearly expressed this philosophy about science--evidence, in this view, functions only to disprove theories which aren't true.

In this way, mathematical rationalism has made only small concessions to the Lockean

democratic philosophy that things are new, open, and flexible. Several other mental habits have been attached to the neokantian mainstream of science, such as the deep assumption of the ultimate randomness of nature, and the preference for the simplest mechanical models of how nature works, because simple mechanical models are the easiest to relate to the mathematical description of their behavior, their "laws."

This philosophical context has given special power to an idea of "one-to-one correspondence" (and to a related idea of an "all-or-nothing" response). Its overtones are everything--it implies exactness, completeness, perfection. One stimulus produces one nervous discharge, for example, and nothing else--if you set your apparatus up in such a way that it can't measure anything else, and if you define a "stimulus" as something which produces a nervous discharge. The "one-to-one" idea helps to sustain the mechanical models which make the mathematical hypotheses easier to manage. In genetics, one "gene" corresponded to one "trait," because the system was defined in that way, not because organisms were usually constituted in that way. Traits, like nerve reactions, had to be all-or-nothing--the offspring of a red-flowered plant and a white-flowered plant weren't allowed to be pink, because a discrete mechanical theory didn't want to recognize such confusing things.

In sensory physiology, a unit of stimulus, for example a photon of light, was "transduced" into a unit of response, by some object in the cell which changed one form of energy into another. The "one-to-one correspondence" idea, working in terms of a discrete transducer in the cell, led our scientific establishment during almost the entire 20th century to say that it was impossible in principle for radio waves, ordinary sound waves, red light, or "subthreshold" x-rays to have any "biological effects" at all. The gigantic amount of stupidity involved in this can probably be taken as a hint that there is a fundamental flaw in our scientific-philosophical culture.

It was these contexts, in genetics and nerve physiology particularly, that led to the confidence that there would be a "discrete" (i.e., simple mechanical) thing in certain cells which would

allow the "female hormone" to produce its effect, the "female response."

Passing quietly over the questions of whether estrogen is "the female hormone" and whether there is a discrete female response to be elicited by estrogen, we can think about the meaning of the existence of a protein in the cell which is the receptor and transducer of the molecular signal of the hormone. If there are many copies of the "female gene" to be activated, and if there are many copies of the receptor molecule, then the response to estrogen can be graded from small to maximum, according to whether there are only a few molecules of estrogen reaching the cell, or enough molecules to "saturate" all the "female genes" with the appropriate number of estrogen-activated receptor molecules. When the dose of estrogen is high enough to saturate all of the estrogen-responsive genes or all of the estrogen receptor molecules, higher doses of the hormone will have no more effect.

For years, some researchers were finding exactly what they had predicted. Before estrogen was applied to the cell, all of the "receptors" were found in the cytoplasm, none in the nucleus. When estrogen was applied, the receptor bound the estrogen and changed its shape, and was then transported into the nucleus, leaving none in the cytoplasm. After a time, the receptor and the estrogen that was bound to it, activated certain genes, which began transcribing specific RNA, which then moved to the cytoplasm, where it was used to produce the proteins which embodied the "estrogen response."

But as more people studied the system, none of those events stayed as simple as the early studies had indicated. Especially studied at the normal body temperature, the "receptors" appeared to be in a fully activated state *without* estrogen. Some of them disappeared at body temperature; different techniques produced different results, and the receptors were probably already distributed throughout the cell before estrogen was added to the system. When the system was held at nearly the freezing temperature, the added estrogen had the anticipated action. Although some of the experimental results are hard to relate to the supposed biological

actions of the receptors, the alteration of these proteins by estrogen in a cold system is interesting in itself, since it indicates that estrogen changes the stability of the proteins when the watery solution is close to its freezing point, something which might be applicable to many other proteins, and which could have important implications for the way estrogen acts. The "cold-sensitive" receptors, like certain enzymes and structural proteins, apparently respond sensitively to the *entropy of their watery environment*, which suggests that they could participate in a cooperative holistic regulatory system.

In the 1960s, endocrine physiologists were already pointing out that *many different things bound estrogen, that some of those things responded instantly to the presence of estrogen, and that estrogen began producing its biological effects instantly when it entered the cell, and many cellular and organismic effects of estrogen were continuously graded from the smallest dose to the largest doses, with no evidence of "saturability."* If Popper's philosophy of science really represented how science works, the massive evidence that conflicted with the "estrogen receptor" theory would have disproved that theory. But the practical way to deal with evidence that doesn't measure up to the model is to ignore it.

A few researchers, mainly people who studied nerves and believed that nerves were governed by their "membrane functions," noticed the evidence for estrogen's instantaneous effects, and began describing these as estrogen's "membrane effects." But these people, too, generally thought in terms of discrete and saturable "membrane estrogen receptors."

The same model of cellular action by discrete "response elements" that led so many people to deny the biological effects of electromagnetic radiation has served the medical-pharmaceutical establishment's desire to maintain that they understand and can control estrogen's potential for harm.

Estrogen was said to be able to promote, but not to initiate, cancer, and to do that only in the

"female organs" (uterus and breasts) which contained the estrogen receptors.

The abstract "classical estrogen receptor" model is a rationale behind the tens of millions of unnecessary hysterectomies that have been performed in the United States, and it is part of the argument for removing breasts to prevent cancer, and for ignoring the multitude of other harmful effects that estrogen can have.

Large doses of estrogen were said to be harmless, because the response system was saturable, and beyond a certain dose, additional estrogen could have no effect..

According to the idea that estrogen acts only through "its receptor," it shouldn't change the activity of existing enzymes, or immediately increase the cell's affinity for water, or modify ionic balances, or act on mitochondria, or cause mutations, or produce massive amounts of free radicals, or accelerate cellular aging, or cause an unsaturable, dose-related increase in active electrons (as measured by their reaction with an indicator-dye), or cause inflammation, or epileptic seizures, or produce birth defects, or activate the stress/shock proteins such as the "heat shock proteins," or disrupt microtubules, or disorganize the mitotic apparatus in a dose-related manner, up to the point that it produces genomic instability, three-cornered cell division, loss or gain of chromosomes, multipolar cell divisions, and finally cellular disintegration. None of those effects is predicted by the idea of the receptor-transducer of femininity, and so "the female hormone" shouldn't produce them.

If a physiological level of estrogen produces, in a dose-related manner, functional and anatomical changes in many parts of many kinds of cell in many organs, in both men and women, independently of "the estrogen receptor," then a thoroughly different approach to understanding the sensitivity and response to estrogen is needed.

Many different tissues contain the protein that is called the "estrogen receptor"--liver, kidney, thymus, pancreas, stomach, bowel, brain, retina, lung, skin, gums, etc., so--ignoring the responses which don't require that protein--the original intent of the "estrogen receptor" theory has

become pretty muddled, unless it can, for example, explain that there is something sexually relevant in a woman's gums. And men's tissues have the "estrogen receptors" just as widely distributed, so the "specific response" idea has become so difficult to sustain that it is slowly coming to be held that the estrogen receptor does something different in different tissues, and under different circumstances. But at that point, the silliness of calling it "the estrogen receptor" should start to become apparent. It would seem to be just one more of the many things which respond to estrogen.

Estrogen produces many effects without the "receptor," and when the receptor is "activated," what it does, wherever it is, still hasn't been satisfactorily defined.

Rather than pretending that estrogen's many effects just don't exist, a few people have looked for ways to find order and generality in the complex diversity.

Szent-Gyorgyi's career was devoted to finding some integrating simplicities that would make it possible to understand the "living state," which he saw as a special state of matter which corresponded to certain ways of using energy. For most of his career, a central question was how the special state of water in the cell helped to sustain certain active electronic states. At one point, he studied the ways in which estrogen and progesterone oppositely affected the physiology of the heart; he obviously wasn't treating them as "female hormones."

Influenced by Szent-Gyorgyi, in 1971 and 1972 I proposed that estrogen, by influencing the cell's water-structure in a particular way, could in an organized way alter the function of a large number of enzymes and physiological processes. The change of water structure induced by estrogen is analogous to "melting," and this type of change, a loosening of the structure of the water, can be seen to occur in a variety of other cellular states, for example, in cancer, aging, and lack of oxygen. Articles by Troshin, Cope, Damadian, Wiggins, Clegg, Drost-Hansen, and Ling discuss the issue of the difference of cell-water from ordinary bulk-water.

Going back to the old ideas of radical empiricism, it was the whole animal (or the whole cell) which experienced; experience wasn't reduced to "sensory atoms" which activated inner structures one unit at a time. (Sensory atomism was given a strong foothold in science when Einstein proposed the quantum interpretation of the photoelectric effect; that theory was conditioned by the same philosophical environment.) Theories of "the living state" represent attempts to bring empirical reality back into science, examining what happens in reality rather than what can be found that corresponds to the convenient units of our favorite way of calculating.

In its long history, the theory of the estrogen receptor hasn't produced any demonstrable benefits, except to the drug industry. (Tamoxifen, useful for its antiestrogen effect, is active even without the estrogen receptor.) Even the idea of using the estrogen receptor idea in cancer prognosis has proven to be little more than a fantasy. But the idea *has* produced a great amount of harm, allowing the drug experts to assure the public that they understand where estrogen's risks and benefits lie, just as the x-ray experts used to assure the public that "low doses" of radiation couldn't cause cancer, or brain damage, or birth defects.

When someone speaks "knowledgeably" about "estrogen receptors," it is important to ask just what they mean, and what evidence supports their claims.

Language matters. The doctrine of "the female hormone" acting through "its receptor" is being used to sell drugs. They say estrogen delays aging, and if one estrogen causes cancer, they will provide a "designer estrogen" or a "specific antiestrogen" to prevent or cure cancer.

Ordinary estrogens are being promoted to prevent osteoporosis, heart disease, and (though they don't yet make direct product claims in this case) Alzheimer's disease and other degenerative brain diseases. **If estrogen is protective against these diseases, why is the incidence of osteoporosis and Alzheimer's disease so much higher in women than in men?** And why is the incidence of bone fractures caused by osteoporosis

increasing, even among men, who are now being exposed to more estrogen than in the past?

For a long time, estrogen was sold to "prevent miscarriages," despite the clear evidence that it caused them. The language of deceitful salesmanship made that possible, since "the female hormone" had to support "the female function" of child-bearing. When the industry realized that it would eventually be able to sell the product to prevent child-bearing, it invented a ridiculous rationale, claiming that *taking* estrogen acted to *lower* estrogen and prevent conception. But the side effects of having too much estrogen forced them to lower the dose of estrogen, and this was occurring at the same time that the estrogen pill was supposed to be lowering the body's estrogen level. Essentially, the industry will say anything that the public will swallow, and the public will swallow a lot.

When patents on one generation of drugs expire, the industry prepares the public for a new generation of better drugs, by "educating" them in the new uses of the language. The language and ideology of the "estrogen receptor" is like the patter of a prestidigitator, distracting the audience from the real issue: Is the drug going to be helpful or harmful?

If we are free of the Receptor Dogma, we can think of controlling estrogen's effects by means other than by making molecules to block estrogen's binding to its receptor, or making molecules to bind to "antiestrogen receptors."

It is now clear that estrogen is intimately related to the universal stress-reaction system, the heat shock proteins. Progesterone, the most direct and general antagonist to estrogen, is now seen to be involved in this fundamental system—it opposes the actions of the stress proteins, and the stress proteins mediate the factors which cause a progesterone deficiency.

The problem of allowing estrogen to have its useful effects, without causing cumulative harm, such as aging the brain and bringing on menopause, is essentially a problem of achieving optimal functioning without stress. The problem

has to do with the organism in its environment, not with specific "designer drugs."

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low-affinity D2 DA agonist binding sites and of the sum of high + low agonist DAergic agonist binding densities as detected by apomorphine competition of [³H]spiperone binding. By contrast, a significant conversion of high into low agonist affinity binding states was seen at 15 min (38.6% of conversion, P less than 0.05) and 30 min (40.0% of conversion, P less than 0.01) after the acute physiological steroid injection. Thus, very small doses of estradiol were able to rapidly increase DA turnover and modulate the striatal agonist affinity states of the D2 DA receptor. This effect of estradiol is probably non-genomic, presynaptic and may involve a membrane effect at the DA autoreceptor level."

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CA1 pyramidal neurons (n = 86) were investigated utilizing intracellular recording from the rat hippocampal slice preparation. Bath application of 17 beta-estradiol, but not 17 alpha-estradiol, caused a reversible depolarization and increased input resistance with a latency of less than 1 min in 19.8% of CA1 neurons tested. There was no significant difference in the percentage of estradiol-responsive cells between male and female rats. Estradiol-responsive cells were identified from prepubertal female rats, as well as females in all stages of the estrous cycle. 17 beta-estradiol had no effect on the slow afterhyperpolarization or accommodative properties of CA1 neurons. In 2 out of 4 cells tested, the specific antiestrogen, tamoxifen, blocked the excitatory response to 17 beta-estradiol.

Rom J Endocrinol 1993;31(1-2):41-8 The role of catecholamines in the distribution of steroid hormones in the striated and cardiac muscle. Burtea C, David A, Butnaru F. Loss of muscular strength is a well-known component of the clinical picture many endocrine diseases and is often their predominant aspect. It has recently been proved that the cytoplasmatic receptors for steroid hormones (SH) are artefacts of the fixation techniques and that they are attached to the internal surface of the cell membrane. Our experiment was made on male and female. Wistar rats which were tested for the level of radioactively labelled steroid hormones (³H and HD³H hydrocortisone; ³H testosterone, TS³H; ³H estrone, FS³H) in various types of skeletal muscles (from rapid to slow) and cardiac muscle before and after adrenalin administration. Before adrenalin administration one noticed: (a) a significantly higher level of HD³H (p < 0.05) in the female skeletal muscle; (b) in the femoral biceps and psoas, a significantly higher distribution of TS³H in males (p < 0.01), whereas in the diaphragm and the heart, there were no significant differences between sexes; (c) there are significant differences between sexes as regards the ES³H level in any of the studied muscles. After adrenalin administration there was a significant decrease in the level of labelled SH uptake in all experimental schemes. It is possible that adrenalin block the HS diffusion through the plasma membrane or even their binding to specific receptors.

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nervous tissue results in a rapid change of membrane potential (60, 71). Such a rapid effect is not likely to be the consequence of nuclear action, but rather must be related to events occurring on the cell surface. It has been hypothesized that sex steroids affect the fluidity of the cell membrane, therefore modifying the ion transport or neurotransmitter receptor activity (142). If this were the case we would expect to observe a similar effect after application of any steroid. Experimental evidence demonstrates that not all the steroids affect the nervous membrane potential. Moreover, two steroids, estradiol and progesterone, have been described to modulate membrane potential in an opposite way (66, 67, 69, 75). At the moment, there is no evidence for the presence of steroid receptors on neuronal membranes which could mediate the described phenomena."

Science 1986 Jul 11;233(4760):226-8 Mechanism of the rapid effect of 17 beta-estradiol on medial amygdala neurons. Nabekura J, Oomura Y, Minami T, Mizuno Y, Fukuda A The mechanism by which sex steroids rapidly modulate the excitability of neurons was investigated by intracellular recording of neurons in rat medial amygdala brain slices. Brief hyperpolarization and increased potassium conductance were produced by 17 beta-estradiol. This effect persisted after elimination of synaptic input and after suppression of protein synthesis. Thus, 17 beta-estradiol directly changes the ionic conductance of the postsynaptic membrane of medial amygdala neurons. In addition, a greater proportion of the neurons from females than from males responded to 17 beta-estradiol.

J Steroid Biochem 1988;30(1-6):195-207 The cellular effects of estrogens on neuroendocrine tissues. Naftolin F, MacLusky NJ, Leranth CZ, Sakamoto HS, Garcia-Segura LM Estrogen action on sensitive neurons in the rat diencephalon has been studied by morphologic techniques; evidence of estrogen action at every level is presented, including tracts, cells, circuitry and subcellular organelles. The demonstration in the arcuate nucleus of estrogen-induced synaptic remodelling, estrogen-induced postsynaptic membrane phenotypes, changes in intracellular membranes and rapid estrogen actions on neuronal endo-exocytosis indicates that cellular estrogen actions may underlie the neuronal control of reproduction.

Neuroendocrinology 1988 Apr;47(4):294-302 Inhibition of hypothalamic and pituitary muscarinic receptor binding by progesterone. Klangkalya B, Chan A. "The inhibitory effect of progesterone was rapid, reversible, and not dependent on divalent metal ions (Ca²⁺, Cu²⁺, Fe²⁺, Mg²⁺, Mn²⁺, and Zn²⁺.)"

Res Commun Chem Pathol Pharmacol 1988 Apr;60(1):141-4 Clomiphene blocks the effect of intravenous estradiol on the firing rate of rat nigral dopamine neurons. McCall WV, Ellinwood EH Jr, Nishita JK, Lee TH Intravenous 17-beta-estradiol (BETA) has a potent,

stereo-specific, and rapid effect on dopamine (DA) neuron firing rate in the substantia nigra compacta (SNC). Our data demonstrate that immediate intravenous pretreatment with the anti-estrogen clomiphene (CLOM) blocks the action of subsequent intravenous BETA administration. Our results provide further physiologic evidence for membrane-bound estradiol (E2) receptors within the rat brain.

Neurosci Lett 1988 May 16;88(1):113-8 Rapid conversion of high into low striatal D2-dopamine receptor agonist binding states after an acute physiological dose of 17 beta-estradiol. Levesque D, Di Paolo T "Ovariectomized female rats injected with 17 beta-estradiol (100 ng, s.c.) showed, as previously observed, an increase of the dopamine (DA) metabolites dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) with no change of DA concentrations in the striatum. This increase was observed as soon as 15 min following the injection while plasma estradiol reached a peak of 78 pg/ml after 5 min and was significantly elevated until 45 min to ultimately return to control values at 60 min." "Thus, very small doses of estradiol were able to rapidly increase DA turnover and modulate the striatal agonist affinity states of the D2 DA receptor. This effect of estradiol is probably non-genomic, presynaptic and may involve a membrane effect at the DA autoreceptor level."

Neuroendocrinology 1992 Jan;55(1):1-8 Progesterone promotes rapid desensitization of alpha 1-adrenergic receptor augmentation of cAMP formation in rat hypothalamic slices. Petitti N, Etgen AM "We previously demonstrated that norepinephrine (NE) induction of cAMP accumulation in slices of the preoptic area (POA) and middle hypothalamus (MH) is reduced by in vivo administration of progesterone to estradiol-primed rats, apparently by eliminating alpha 1-receptor augmentation of beta-receptor-stimulated cAMP formation. The present studies examined whether in vitro exposure to progesterone would also depress NE-stimulated cAMP synthesis. POA and MH slices from estradiol-primed females were incubated with 20 nM progesterone for 5-30 min prior to addition of 100 microM NE. Pre-incubation of slices with progesterone for as little as 5 min significantly suppressed NE-stimulated cAMP formation by greater than 60%." "These data indicate that progesterone may have rapid, non-genomic effects on alpha 1-adrenergic receptor coupling to second-messenger systems in the hypothalamus of female rats."

J Neurosci 1996 Jan 15;16(2):595-604 Estradiol reduces calcium currents in rat neostriatal neurons via a membrane receptor. Mermelstein PG, Becker JB, Surmeier DJ Neuroscience Program, University of Michigan, Ann Arbor 48104, USA. Until recently, steroid hormones were believed to act only on cells containing intracellular receptors. However, recent evidence suggests that steroids have specific and rapid effects at the cellular

membrane. Using whole-cell patch-clamp techniques, 17 beta-estradiol was found to reduce Ba²⁺ entry reversibly via Ca²⁺ channels in acutely dissociated and cultured neostriatal neurons. The effects were sex-specific, i.e., the reduction of Ba²⁺ currents was greater in neurons taken from female rats. 17 beta-Estradiol primarily targeted L-type currents, and their inhibition was detected reliably within seconds of administration. The maximum reduction by 17 beta-estradiol occurred at picomolar concentrations. 17 beta-Estradiol conjugated to bovine serum albumin also reduced Ba²⁺ currents, suggesting that the effect occurs at the membrane surface. Dialysis with GTP gamma S prevented reversal of the modulation, suggesting that 17 beta-estradiol acts via G-protein activation. 17 alpha-Estradiol also reduced Ba²⁺ currents but was significantly less effective than 17 beta-estradiol. Estradiol and 4-hydroxyestradiol were found to reduce Ba²⁺ currents with similar efficacy to 17 beta-estradiol, whereas estrone and 2-methoxyestriol were less effective. Tamoxifen also reduced Ba²⁺ currents but did not occlude the effect of 17 beta-estradiol. These results suggest that at physiological concentrations, 17 beta-estradiol can have immediate actions on neostriatal neurons via nongenomic signaling pathways.

Exp Cell Res 1997 Jun 15;233(2):274-80 Mitochondrial membrane potential changes in osteoblasts treated with parathyroid hormone and estradiol. Troyan MB, Gilman VR, Gay CV. "For estradiol, half of the cells responded at a significant level, with a membrane potential reduction of 6 to 13% being recorded; the other half did not respond. Thyroxine did not alter mitochondrial membrane potential. Responses were detectable within 20 s for valinomycin, but occurred at a slower rate, over 200 to 300 s, following PTH and estradiol treatment. Responses to PTH and estradiol could be due to mitochondrial uptake of cytosolic Ca²⁺."

Can J Cardiol 1997 Nov;13(11):1093-100 Reversible inhibition of gap junctional communication elicited by several classes of lipophilic compounds in cultured rat cardiomyocytes. Verrecchia F, Herve JC. **BACKGROUND:** Electrical coupling between cardiac muscle cells is mediated by specialized sites of plasma membrane termed 'gap junctions', which consist of clusters of transmembrane channels that directly link the cytoplasmic compartments of neighbouring cells and allow direct transfer of small ions and molecules. These structures provide low resistance electrical pathways between cardiac cells, necessary for rapid impulse propagation and, thus, coordinate contraction of the myocardium." "Short term (15 min) exposures to some of these lipophilic compounds led, in a concentration range 1 to 22 microM, to a reversible inhibition of cell to cell communication. None of these uncoupling treatments altered the cytosolic calcium concentration, examined by means of a fluorescence indicator. The uncoupling effect of sex hormones persisted in the presence of blockers of their respective nuclear receptors (eg, cyproterone acetate for testosterone and tamoxifen for

17-beta-estradiol). Some of these blockers (tamoxifen, clomiphene) were able to impair gap junctional communication, whereas others (nafoxidine and cyproterone acetate) had no effect." "Several lipophilic compounds able to hinder cell to cell communication have also been seen to affect voltage-activated or ligand-activated ionic channels. Lipophilic molecules with an appropriate molecular skeleton could insert into the membrane, with resulting destabilization and unspecific closure of membrane channels."

Brain Research Bulletin, 1988 Feb, 20(2):151-5. Phillis JW; O'Regan MH. **Effects of estradiol on cerebral cortical neurons and their responses to adenosine.** "17 beta-Estradiol antagonized the inhibitory actions of adenosine 5'-N-ethylcarboxamide on 76% of the neurons tested, but did not enhance the actions of this uptake resistant adenosine analog." "It is suggested that . . . 17 beta-estradiol is also able to antagonize the actions of these purines. Antagonism of the effects of endogenously released adenosine may account for the excitant actions of 17 beta-estradiol on the central nervous system."

Breast Cancer Res Treat 1995;36(3):299-306 Tamoxifen elicits rapid transmembrane lipid signal responses in human breast cancer cells. Cabot MC, Zhang ZC, Giuliano AE John Wayne Cancer Institute, Saint John's Hospital and Health Center, Santa Monica, CA 90404, USA. "The antiestrogen tamoxifen competes with estrogen for receptor occupancy, although reports indicate that not all effects of tamoxifen are mediated via this specific interaction. In the present study we sought to determine whether tamoxifen can initiate transmembrane lipid signals." "It is therefore suggested that some actions of tamoxifen are mediated by promoting production of second messenger lipids that elicit transmembrane signal transduction cascades. This view is in line with ideas on non-estrogen receptor associated actions of tamoxifen by way of alternate binding sites."

Endocrinology 1995 May;136(5):2341-4 Estradiol-17 beta and mu-opioid peptides rapidly hyperpolarize GnRH neurons: a cellular mechanism of negative feedback? Lagrange AH, Ronnekleiv OK, Kelly MJ

Environ Health Perspect 1995 Oct;103 Suppl 7:41-50 The other estrogen receptor in the plasma membrane: implications for the actions of environmental estrogens. Watson CS, Pappas TC, Gametchu B "Environmental or nutritional estrogenic toxicants are thought to mediate developmental and carcinogenic pathologies. Estrogen receptor (ER) measurements are currently used to predict hormonal responsiveness; therefore all ER subpopulations should be considered. We have been involved in the immunoidentification and characterization of membrane steroid receptors in several systems and have recently shown that binding of estradiol (E2) to a subpopulation of ERs (mER) residing in the plasma

membrane of GH3 pituitary tumor cells mediates the rapid release of prolactin (PRL)." Here we review these findings and present other important characterizations of these receptors such as trypsin and serum susceptibility, movement in the membrane, confocal localization to the membrane, binding to and function of impeded ligands, and immunoseparation of cells bearing mER. We plan to use this system as a model for both the physiological and pathological nongenomic effects of estrogens and estrogenic xenobiotics. Specifically, it should be useful as an in vitro assay system for the ability of estrogenic xenobiotics to cause rapid PRL release as an example of nongenomic estrogen effects.

J Neurosci 1996 Jun 1;16(11):3620-9 **17 beta-Estradiol potentiates kainate-induced currents via activation of the cAMP cascade.** Gu Q, Moss RL "Evidence for nongenomic actions of steroids is now coming from a variety of fields of steroid research. Mechanisms of steroid action are being studied with regard to the membrane receptors and the activation of second messengers. The present study investigated the mechanism for the rapid effect of estrogen on acutely dissociated hippocampal CA1 neurons by using the whole-cell, voltage-clamp recording." "The potentiation by 17 beta-estradiol was similar to the enhancement of kainate-induced currents evoked by 8-bromo-cAMP, and was modulated by an inhibitor of phosphodiesterase (IBMX)." "The data suggest that the potentiation of kainate-induced currents by 17-beta-estradiol was likely a G-protein(s) coupled, cAMP-dependent phosphorylation event. By involvement of this non-genomic mechanism, estrogen may play a role in the modulation of excitatory synaptic transmission in the hippocampus."

Eur J Endocrinol 1996 Sep;135(3):367-73 **17 beta-estradiol stimulates a rapid Ca²⁺ influx in LNCaP human prostate cancer cells.** Audy MC, Vacher P, Duly B "Prostate growth is known to be controlled by steroids such as androgens and estradiol." "In view of the pivotal role played by Ca²⁺ ions in cell proliferation, we decided to investigate the effects of 17 beta-estradiol (E2) on intracellular calcium concentration ([Ca²⁺]_i) in a human prostate tumor cell line, LNCaP. In this study, we show that E2 induced a dose-dependent (0.1-100 nmol/l) influx of Ca²⁺ in these cells. These effects occurred rapidly after the beginning of the ejection and were maintained in the presence of the hormone (plateau phase)." "Our results suggest the existence of E2 binding sites at the plasma membrane surface of LNCaP cells, linked to calcium signalling and, more specifically, Ca²⁺ channels."

Recent Prog Horm Res 1997;52:33-68; discussion 68-9 **Estrogen: nontranscriptional signaling pathway.** Moss RL, Gu Q, Wong "The long-term, genomic actions of estrogen and other steroid hormones are now relatively well understood. In this process, steroids bind to a cytoplasmic/nuclear receptor and the hormone receptor complex that, in turn, binds to DNA and triggers

RNA-dependent protein synthesis. This process produces a response over time periods of several minutes to hours to days. Estrogen also exerts a variety of short-term effects (observed in milliseconds to minutes) on target organs that are not compatible with the classical genomic mechanism. These short-term, nontranscriptional actions are thought to be neuromodulatory in nature and critical for cell-cell communication."

Recent Prog Horm Res 1997;52:71-99; discussion 99-101 **Nongenomic actions of steroids on gonadotropin release.** Wiebe JP "The release of gonadotropins is effected by GnRH and regulated by steroids. The classical mechanism of steroid hormone action, which implies the binding of hormone receptor complexes to regulatory elements of nuclear genes, is derived largely from the well-studied and familiar steroids such as progesterone, testosterone, and estradiol. Their effects on gonadotropin release generally have been examined following hours or days of exposure and therefore cannot account for the rapid effects of steroids on gonadotropin release."

Exp Cell Res 1997 Jun 15;233(2):274-80 **Mitochondrial membrane potential changes in osteoblasts treated with parathyroid hormone and estradiol.** Troyan MB, Gilman VR, Gay CV.

Invest Ophthalmol Vis Sci 1998 Oct;39(11):2105-10, **Estrogen receptor expression in bovine and rat retinas.** Kobayashi K, Kobayashi H, Ueda M, Honda Y.

Am J Pathol 1998 Aug;153(2):469-80 **Cellular distribution of retinoic acid receptor-alpha protein in serous adenocarcinomas of ovarian, tubal, and peritoneal origin: comparison with estrogen receptor status.** Katsetos CD, Stadnicka I, Boyd JC, Ehya H, Zheng S, Soprano CM, Cooper HS, Patchefsky AS, Soprano DR, Soprano KJ **Retinoids are effective growth modulators of human ovarian carcinoma cell lines. Their effects are mediated by nuclear retinoic acid receptors (RARs) and retinoid X receptors (RXRs), which are transcriptional factors and members of the steroid/thyroid receptor superfamily.** To our knowledge, until now, the cellular distribution of RAR proteins in human ovarian tumor specimens is unknown. This study provides new data on the differential cellular localization of RAR alpha protein in 16 serous adenocarcinomas originating from the ovaries, fallopian tubes, and the peritoneum. Using an affinity-purified antiserum specific for RAR alpha and a monoclonal antibody recognizing the full-length estrogen receptor molecule (clone 6F11), we performed immunohistochemistry on frozen tissue sections and examined the relationship between RAR alpha and estrogen receptor protein expression by comparing the percentage of immunostained tumor cells for either receptor. Our findings indicate a strong linear relationship between the percentages of RAR alpha- and estrogen receptor-labeled tumor cells as determined by linear regression analysis ($P < 0.005$, $r =$

0.825). A modest inverse relationship was found between the percentage of RAR alpha-positive tumor cells and histological grade, attesting to a differentiation-dependent trend ($P < 0.04$). No significant relationship was found between RAR alpha-labeled cells and clinical stage ($P = 0.139$), site of tumor origin (ovaries versus fallopian tubes versus peritoneum) ($P = 0.170$), and primary versus metastatic lesion ($P = 0.561$). Thus, serous adenocarcinomas are capable of expressing RAR alpha and estrogen receptor despite high histological grade and advanced stage of neoplastic disease. Compared with the heterogeneous localization of RAR alpha in cancer cells, there was widespread RAR alpha immunoreactivity in tumor-infiltrating lymphocytes, vascular endothelial cells, and stromal fibroblasts, underscoring the value of immunohistochemistry in the accurate determination of RAR/(RXR) content in tumor specimens.

Cancer 1998 Apr 15;82(8):1495-500 Estrogen-receptor-related protein p29 in primary nonsmall cell lung carcinoma: pathologic and prognostic correlations. Vargas SO, Leslie KO, Vacek PM, Socinski MA, Weaver DL "In this study, immunohistochemical expression of estrogen receptor (ER) and the ER-related protein p29 was correlated with survival of patients with nonsmall cell carcinoma of the lung. The relation between p29 expression and survival time was different for men and women. A statistically significant negative relation for women was observed; this relation was most pronounced in patients with Stage I and II tumors. A positive but not statistically significant relation was observed for men. CONCLUSIONS: The ER-related protein p29 commonly is expressed in nonsmall cell carcinomas of the lung."

Anticancer Res 1997 Jul-Aug;17(4A):2577-81. Immunocytochemical detection of prostate specific antigen expression in human breast carcinoma cells. Bodey B, Bodey B Jr, Kaiser HE. "To date, no true tissue specific antigen has been discovered. Prostate-specific antigen (PSA) was initially reported to be a tissue specific protein, detected in the seminal fluid and produced by normal and abnormal epithelial cells of the prostate gland." "We observed the presence of PSA in all 16 BC cases, and this expression was independent of estrogen receptor status. The intensity of the staining was moderate to high (B to A) and localized to 20% to 40% of the total BC cell population...." "The prognostic significance of PSA in BCs may lie in the identification of a subset of estrogen receptor negative BC patients who have malignancies associated with a good prognosis."

DNA Cell Biol 1998 Sep;17(9):743-50 Thyroid hormone receptor is a negative regulator in p53-mediated signaling pathways. Barrera-Hernandez G, Zhan Q, Wong R, Cheng SY "Thyroid hormone nuclear receptors (TRs) are ligand-dependent transcription factors which regulate growth, differentiation, and development. The molecular mechanism by which TRs mediated these

effects remains unclear. A prevailing hypothesis is that TRs exert their biological effects by cooperating with other transcription factors. We have recently shown that the human TR subtype beta1 (hTRbeta1) interacts with the tumor suppressor p53, which plays a critical role in cell-cycle regulation and tumorigenesis."

Lab Invest 1998 Jun;78(6):699-706 Expression of the 150-kd oxygen-regulated protein in human breast cancer. Tsukamoto Y, Kuwabara K, Hirota S, Kawano K, Yoshikawa K, Ozawa K, Kobayashi T, Yanagi H, Stern DM, Tohyama M, Kitamura Y, Ogawa S "The 150-kd oxygen-regulated protein (ORP150) is a novel endoplasmic reticulum-associated polypeptide in the HSP70 family. In view of links between expression of HSPs/ORPs and tumor properties, especially tumor invasiveness and resistance to therapeutic regimens, expression of ORP150 in human breast cancers was examined." "These results suggest that ORP150 is up-regulated in tumors and, in breast tumors, may be associated with tumor invasiveness."
