Why Drugs and Hormones May Interact in Psychiatric Disorders

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Issue: *Neurotransmitter receptors are found in the neuronal membrane and trigger biochemical signals from the outer membrane through the cytoplasm and ultimately to the genome. Receptors for numerous steroid hormones, however, act directly at the genome. These 2 pathways to the genome apparently interact, and their "cross-talk" may be an important factor in normal neuronal functioning as well as in psychiatric disorders and the actions of psychotropic drugs.*

Receptors most familiar to psychiatrists and psychopharmacologists may be those located in the neuronal membrane that normally interact with monoamine neurotransmitters.[1] These include the 12 transmembrane region neurotransmitter transporters (e.g., the serotonin transporter or "serotonin reuptake pump") that are the targets of most known antidepressants, including the selective serotonin reuptake inhibitors (SSRIs). Other well-recognized neuronal membrane receptors include the superfamily of 7 transmembrane region G protein–linked second messenger systems that are directly or indirectly the targets of many other psychotropic drugs, such as antipsychotics, some anxiolytics (e.g., buspirone), some antidepressants (e.g., mirtazapine), and many more.[2] Still other well-known receptors located in the neuronal membrane include the superfamily of ligand-gated ion channels, such as those for glutamate and γ-aminobutyric acid (GABA), and are the targets of psychotropic drugs such as PCP (phencyclidine) and benzodiazepines (Table 1).

The Superfamily of Nuclear Ligand-Activated Transcription Factors

By contrast, another important class of receptors has well-known actions in peripheral tissues and functions in the central nervous system (CNS) that are gaining increasing attention. This particular type of receptor does not exist in cell membranes, but comprises a very large group of receptors known as "nuclear ligand-activated transcription factors" that act directly at the genome in the cell nucleus.[3,4]

The nuclear ligand-activated transcription factors include the steroid receptors for estrogen, progesterone, androgen, glucocorticoids, and mineralocorticoids. They also include receptors for thyroid hormone, retinoids, and vitamin D. These receptors play a key role in turning genes on (as transcriptional activators) and off (as transcriptional repressors). Such genetic regulation plays a central role in essentially all aspects of biological functioning, from development to metabolism to reproduction to behavior. Some of the most important recent insights into CNS functioning from this superfamily may come from the steroid receptors such as those for estrogen (to be covered in next month's feature).

How Do Membrane and Nuclear Receptors Work?

Neurotransmitters turn genes on by activating proteins known as transcription factors via their receptors, which are often members of the G protein–linked superfamily. A com-

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Table 1. Receptors and Ligands[a]

Receptor Superfamily	Receptor	Natural Ligand	Drug Ligand
Membrane-Bound			
Transporter	5-HT transporter	5-HT	SSRIs
	NE transporter	NE	Reboxetine, desipramine
G protein–linked	5-HT_{1A}	5-HT	Buspirone
	α_2-Adrenergic	NE	Mirtazapine
Ligand-gated ion channel	$GABA_A$	GABA	Benzodiazepines
	NMDA glutamate	Glutamate	Phencyclidine (PCP)
Nuclear Ligand-Activated Transcription Factor			
Estrogen	Estrogen	Estrogen	Premarin
Progesterone	Progesterone	Progesterone	Provera
Androgen	Androgen	Androgen	Methyltestosterone
Glucocorticoid	Glucocorticoid	Cortisol	Prednisone
Mineralocorticoid	Mineralocorticoid	Cortisol	Florinef
Thyroid	Thyroid	Thyroxine	Levothyroxine, triiodothyronine
Vitamin D	Vitamin D	Calcitrol	Vitamin D[b]
Retinoid	Retinoid	Retinoids	Vitamin A[b]
Various orphan receptors	Unknown	Unknown	Unknown

[a]Abbreviations: 5-HT = serotonin, GABA = γ-aminobutyric acid, NE = norepinephrine, NMDA = *N*-methyl-D-aspartate, SSRI = selective serotonin reuptake inhibitor.
[b]These ligands are found in the diet or as supplements.

Take-Home Points

- Receptors for familiar neurotransmitters, such as the monoamines serotonin and norepinephrine, are located in neuronal membranes, and include neurotransmitter transporters and G protein–linked receptors that are the targets of many psychotropic drugs.
- Receptors from another large superfamily are not membrane bound and do not activate G proteins, but act directly at the genome in the cell nucleus. Such receptors are the targets of numerous hormones.
- It now appears that both types of receptors trigger events at the genome, and that coparticipation of some neurotransmitters with certain hormones is critical for normal neuronal functioning.

mon method whereby such receptors lead to activation of a transcription factor is by altering the amount of phosphate the transcription factor contains. This is the final stage of a "molecular pony express"[2]: the first messenger neurotransmitter leads to second messenger formation, then to the subsequent hand-off of message from molecular messenger to molecular messenger, traveling from the cell membrane through the cytoplasm to the cell nucleus, where the ultimate mailbox for the message is the genome. The last messenger is a transcription factor, which turns a gene either on or off.

By contrast, once a steroid binds to its receptor (often 2 copies join together), the steroid/protein combination actually becomes a transcription factor that can in turn bind directly to DNA and result in gene transcription.[3,4] This process provides a shortcut to the cell nucleus and genome, and genes can be immediately activated or repressed. Gene transcription, of course, then leads to synthesis first of RNA and then to the synthesis of the protein that the gene encodes.

Interactions Between Neurotransmitters and Steroids Via Their Receptor Actions

The old line of thought was "no steroid, no receptor activation." However, we have recently seen that steroid receptors can be activated in the absence of the steroid, by neurotransmitters and growth factors that lead to steroid receptor phosphorylation and thus receptor activation without the steroid.[3,4] If steroid receptors can be activated with or without steroid, i.e., by steroid or by neurotransmitter, then they are set up to be key integrators of signals from neurotransmitters with signals from hormones. Indeed, this may underlie their hypothesized role in the regulation of numerous normal behaviors as well as abnormal behaviors associated with psychiatric disorders. It may also explain why some hormones have synergistic actions with some drugs that modify neurotransmitters, such as antidepressants with estrogen.[5]

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