

Appendix A14.12

Nuclear Hormone Signaling: A Focus on Steroids

In contrast to the other neuroactive compounds we have discussed thus far, many hormones (including cortisol, gonadal steroids and thyroid hormones) are able to rapidly penetrate into the lipid bilayer membrane due to their lipophilic composition (Kandel et al., 2000). Nuclear receptors are transcription factors that regulate the expression of target genes in response to steroid hormones and other ligands. Approximately 50 nuclear receptors are known to exist, and their structure is defined by a number of signature functional domains. Generally, NRs are comprised of: an amino-terminal activation function, the DNA-binding domain; a hinge region; and a carboxy-terminal ligand-binding domain containing a second activation function (Kandel et al., 2000). Upon activation by a hormone, the steroid receptor-ligand complex translocates to the nucleus, where it binds to specific DNA sequences referred to as hormone responsive elements (HREs), subsequently regulating gene transcription (Mangelsdorf et al. 1995; Truss and Beato, 1993). It is now known that nuclear receptors are markedly regulated by additional “accessory proteins”. Nuclear receptor coregulators are cellular factors that complement their function as mediators of the cellular response to endocrine signals. They are generally divisible into coregulators that promote transcriptional activation when recruited (coactivators), and those that attenuate promoter activity (corepressors). A growing body of data is also demonstrating bidirectional cross-talk between nuclear receptors and GPCRs. Thus, for example, gonadal steroids have long been known to modulate the activity of monoaminergic neurons and receptors. More recently, it has been shown that β adrenergic and dopamine D1 receptors are capable of transactivating glucocorticoid and progesterone receptors respectively.

In addition to the traditional view of steroid hormone action, it is now clear, however, that steroid hormones also have so-called non-genomic effects that include changes in neurotransmitter receptors, other membrane receptors, and second-messenger systems. These effects are less well characterized, but evidence for their existence includes modulation of neural activity in brain areas where there are few, if any, gonadal steroid receptors and evidence exists that estrogen directly and rapidly inhibits calcium channels in neurons (McEwen, 1999; Mermelstein et al., 1996).

Neuroactive steroid is the term used for a steroid that is able to not only bind to their respective intracellular receptor and become rapidly translocated to the nucleus, but is also able to alter neuronal excitability via interactions with certain neurotransmitter receptors (Rupprecht, 2003). Many of these abovementioned neuroactive steroids are capable of altering neuronal

excitability by interacting with GABA_A receptors. Studies using chimeras of GABA_A/glycine receptors suggest an allosteric action of neuroactive steroids at the N-terminal side of the middle of the second transmembrane domain of the GABA receptor β 1 and/or α 2 subunits (Rick et al., 1998). However, no direct binding of the steroid to the receptor has been demonstrated. In addition to GABA_A receptors, other members of the ligand gated ion channel family (including 5-HT₃, glycine, nicotinic ACh, and glutamate receptors) have been postulated to represent targets for neuroactive steroids (Rupprecht, 2003).

In view of the GABA_A enhancing potential of 3 α -reduced neuroactive steroids, these steroids have been suggested to possess sleep modulating/promoting (Mendels and Chernik, 1973), anticonvulsant (Frye and Scalise, 2000), anxiolytic (Crawley et al., 1986), and neuroprotective properties (Rupprecht, 2003). Finally, it has been postulated that neuroactive steroids may also contribute to psychiatric symptoms sometimes observed during pregnancy and in the postpartum period (Pearson Murphy et al., 2001).

Table A14.12a

This table summarizes selected peptides and their presumed relevance for psychiatric disorders and their treatment; it is not meant to be an exhaustive listing of findings. It should also be noted that in some cases, e.g. CRF (mood/anxiety), NPY & neurotensin (regulation by medications), oxytocin (affiliative behavior) and orexins (narcolepsy) -- the data is quite convincing. In many of the other examples noted, the evidence must be considered preliminary, but in our opinion quite noteworthy and worthy of further investigation.

Group	Potential Clinical Relevance
Opioid and related peptides	
Endorphin	All these peptides may be involved in opiate dependence/drug abuse; possible antidepressant activity; chronic pain
Enkephalin	
Dynorphin	
Nociceptin	
Gut derived peptides	
VIP (vasoactive intestinal peptide)	Sexual behavior
CCK (cholecystokinin)	Anxiety/panic
Gastrin	Autism?
Secretin	
Somatostatin	Mood disorders and treatment
Tachykinin peptides	
Substance P	NK1 receptor antagonists may alleviate depression/anxiety
Substance K	Regulated by antipsychotics
Neuromedin N	Regulated by lithium

Pituitary peptides

Oxytocin	Affiliative behavior
Vasopressin	Potential novel anxiolytics?
ACTH-adrenal corticotropic hormone	Dysregulated in mood disorders
MSH-melanocyte stimulating hormone	

Hypothalamic releasing factors

CRF-corticotropin releasing factor	Strongly implicated in depressive and anxiety symptoms; potential targets for novel treatments
TRF-thyrotropin releasing factor	Potential antidepressant effects
GHRF-growth hormone releasing factor	

LHRH-luteinizing hormone releasing factor

Others

Calcitonin gene - related peptide	Regulated by ECT and lithium
Angiotensin	Mood disorders/bipolar disorder
Neurotensin	Regulated by antipsychotics and stimulants
Leptin	Satiety signal; involved in diagnosis and treatment induced appetite/wt changes?
CART (cocaine and amphetamine related transcript)	Drug addiction and eating disorders
Galanin	Potentially relevant for Alzheimer's diagnosis and other cognitive disorders
Neuropeptide Y	Potential endogenous anxiolytic; regulated by antidepressants/lithium; reduced by early maternal separation
Orexins/hypocretins	Narcolepsy; sleep abnormalities in other disorders?

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