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Functional Effects of Retinoids in the Adolescent and Adult Central Nervous System

November 19, 2002
Neuroscience Center
National Institute of Mental Health
Rockville, Maryland

BACKGROUND

The goal of this workshop was to exchange information concerning the physiological effects of retinoids in the adolescent and adult central nervous system (CNS) and to stimulate interest in further studies. The workshop was initiated in part as a response to recent reports of depressive-like behavior, aggression, or suicide in adolescents using Accutane. The workshop brought together scientists with expertise in evaluating the developmental, neurochemical, and genetic effects of retinoids with neuropharmacologists possessing expertise in examining the effects of drugs on motivated behaviors, mood, cognition, and aggression. The participants were asked to help assess what research tools are needed to expand the limited knowledge available concerning the possible influences of retinoids on brain circuits regulating mood, cognition, aggression, impulsivity, and other behaviors.

AGENDA

Presentations: Overview of retinoid biosynthesis, metabolism, and actions, with an emphasis on studies potentially relevant to the functional effects of retinoids in the adult central nervous system

1. Bryan Roth, Screening the Receptosome to Uncover Novel Targets for Retinoid Actions
2. Wesley Kroeze, Retinoid-induced Changes in Gene Expression in SH-SY5Y Neuroblastoma Cells
3. Peter McCaffery, The Influence of Retinoic Acid on Hippocampal Cell Division
4. Joseph Napoli, Biosynthesis and Metabolism of Retinoids
5. Thomas Houpt, Neural and Behavioral Effects of Isotretinoin (13-cis-retinoic acid)
6. Irwin Lucki, Sensitivity of Animal Tests for Detecting Depressogenic Activity

Panel discussion

1. Other than the well-known effects of retinoids on CNS embryonic development, what is the scientific evidence that retinoids are functionally important in the mammalian CNS?
2. What specific CNS functions, if any, might one expect to be affected by therapeutic use of systemic retinoids?
3. What types of pre-clinical studies might best address the following issues:
 - a. Effects of chemical form (isomers and metabolites), dose and dosing frequency on CNS function.
 - b. CNS response differences across the lifespan from adolescence through adulthood.
 - c. Possible contribution of retinoid exposure as one of several individual risk factors (genotype, environmental factors, drug/disease interactions, etc) that might alter mood and cognition.
 - d. Pharmacologic interventions that might prevent or ameliorate adverse

effects.

4. What specific research efforts are needed to determine the degree to which retinoids, or genes regulated by retinoids, modulate the activity of brain circuits or signaling pathways that regulate mood, cognition, aggression, impulsivity, and motivated behaviors?

SUMMARY OF RESEARCH ISSUES RAISED DURING THE DISCUSSION

Workshop participants reached consensus that available genetic, behavioral, and neurochemical data are consistent with the idea that retinoids do exert effects in the adult brain. Data were presented that demonstrated *in vitro* effects of retinoids on galanin and alpha5-GABA subunit expression. *In vivo* studies revealed effects of low-dose 13-*cis* retinoic acid administration in rats on neurogenesis in the adult hippocampus. These data were considered suggestive of mechanisms that could account for some possible effects of retinoids on mood and cognition. However, it was generally agreed that knowledge about retinoid expression, function, and regulation in adolescent and adult brains is incomplete and a limiting factor in assessing the impact of retinoid derivatives on brain function including behavior. Moreover, the relevance of the doses, route, and time course of administration of retinoids given in studies of adult animals to that of dosing regimen of Accutane and other retinoids in humans is not known.

NEEDS AND PRIORITIES FOR RESEARCH ON RETINOIDS IN ADULT SUGGESTED BY PARTICIPANTS

Three priority areas were identified for research on retinoids in adult animals:

1. Baseline studies examining the effects of a range of retinoid doses and routes of administration (i.e., oral, systemic injection, central infusion) on neurochemical measures and in models assessing mood, anxiety, aggression, impulsivity, and cognitive function;
2. Pharmacokinetic studies comparing the metabolism of retinoid derivatives in humans and animals;
3. Availability of agonist and antagonists of retinoic acid receptors for use in studies of brain function.

In addition, basic and clinical studies focused on examining the possible combined impact of retinoid exposure with other vulnerability factors for mental illness were suggested as a way to begin to identify individuals at potential risk of adverse CNS effects (e.g., depression, aggression, psychosis) of these compounds.

Several workshop participants expressed interest in conducting additional neurochemical and behavioral studies of retinoids in adult CNS.

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[Top](#)

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