

The Mechanism of "Pruning" in the Human Brain

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The development of the human brain is rapid following birth, reaching about 95 percent of its size by age five to six. The large growth of a baby's brain results from an "over-abundance" of neurons and synapses. These begin to decline around age three; some of the neurons and synapses are "pruned." The remaining neurons and synapses are enhanced by this process.

Another period of enhanced synapse formation occurs just prior to puberty in children in the prefrontal cortex. This is followed by another period of pruning during adolescence. (The foregoing is a compilation of the work of Dr. Jay Giedd, et al., at the National Institute of Mental Health.)

I wish to suggest a mechanism to explain these findings. It is my hypothesis that mammals evolved because of selection for DHEA (Hormones in Mammalian Evolution, Rivista di Biologia / Biology Forum 2001; 94: 177-184). I think primates evolved from mammals because of selection for testosterone within the mammals (ibid, 2002; 95: 319-326). A continuance of selection for testosterone within the primates resulted in humans (Androgens in Human Evolution, Rivista di Biologia / Biology Forum 2001; 94:345-362). I suggest the interaction of these two hormones may explain the enhanced brain of humans as well as the mechanism of "pruning."

It is my primary hypothesis that DHEA optimizes replication and transcription of DNA. Therefore, DHEA will positively affect all tissues. The increases of testosterone during evolution of primates and humans positively affected the ability of some tissues, more than others, to absorb DHEA. I think the most important of these is the brain. This is why the brains of primates and humans are increased in size compared to other mammals. Testosterone stimulates formation of the "androgen receptor" in tissues. DHEA utilizes the androgen receptor.

DHEA is known to "have positive effects on hippocampal CA1 spine synapse density in both sexes (Endocrinology 2004; 145: 4154-61). DHEA "increases the number of newly formed cells [neurons]" even in adult rats (Eur J

The Mechanism of "Pruning" in the Human Brain

Neurosci 2002; 16: 445–53). DHEA promotes neuronal survival following anoxia (Brain Res 2000; 871: 104–12) and may participate in protecting the integrity of synaptic membranes against hyperglycaemia-induced damage? (Biochem Pharmacol 2000; 60: 389–95). Other work suggests that DHEA is involved in the maintenance and division of human neural stem cells. (Proc Natl Acad Sci USA 2004; 101: 3202–7). Testosterone is known to positively affect the brain in some circumstances, not all. I suggest sufficient DHEA must be available to exert positive effects of testosterone in these cases.

DHEA is highest at birth. This is followed by a rapid decline during the first year of life reaching very low levels. DHEA again begins to increase around age three to five, though it is often defined somewhat later (J Clin Endocrinol Metab 2005; 90: 2015–21). I suggest the decline in DHEA is caused by absorption of DHEA by the brain for growth and development at this time. The fetal brain is exposed to maternal testosterone in utero. This induces androgen receptor formation which is used to absorb DHEA for growth and development of the brain. I suggest the rapid growth of a baby's brain is caused by the large amount of DHEA available at birth. Neurons and synapses grow rapidly and luxuriantly because of this DHEA. DHEA is used by the brain at the expense of the rest of the body so DHEA levels decline and other tissues do not develop as rapidly. This is why the brain of babies develops rapidly and their bodies do not. As the brain finalizes its growth and development, the body begins to use increasingly available DHEA for growth and development. This use of DHEA by the body begins to compete with the brain. Neurons that are being activated continue to absorb DHEA readily; neurons that are not activated do not continue to absorb DHEA so they, and their synapses, decline. This may explain the pruning that begins around age three as the body begins to compete for DHEA with the brain.

I suggest all growth and development rely on DHEA. The exposure to testosterone, in male and female fetuses, triggers formation of androgen receptors. These receptors increase the use of DHEA. Hence, testosterone first activates receptors that allow absorption of DHEA. This stimulates growth and development of the brain. Prior to puberty, testosterone, in males and females, again increases. I suggest this exposure to testosterone, again, promotes growth and development of the brain first followed by the body.

The prepubertal testosterone stimulates the final part of brain formation in humans, the prefrontal lobes, to occur. That is, this part of the brain is stimulated to produce androgen receptors in the prefrontal lobes which begin to absorb DHEA. This results in growth of this part of the brain just prior to puberty. This use of DHEA is, again, at the expense of the body. Hence, there is a reduction in growth of the body just prior to puberty. When the growth of the prefrontal cortex is finished, then DHEA is, again, freed for use by the body and the body starts the adolescent growth spurt. This competition for DHEA reduces growth and development of the prefrontal cortex except the areas absorbing sufficient DHEA to remain functional. Therefore, this is a period, again, of pruning of neurons

The Mechanism of "Pruning" in the Human Brain

and synapses that do not absorb sufficient DHEA.

This may also explain why neurons do not increase with age in people. Since DHEA naturally begins to decline around age twenty and testosterone does not resurge, even declines, neurons are not affected by increased androgen receptors and little DHEA is available for absorption and use by neurons.

Testosterone and sufficient DHEA stimulate neuronal growth. Growth, use of DHEA, reduces further growth. Use of DHEA by other tissues reduces maintenance of neurons so pruning of "least-used" neurons occurs.