Joseph Knoll: Enhancer Sensitive Brain Regulations and Synthetic Enhancers (Selegiline, BPAP) Which Counteract the Regressive Effects of Brain Aging

Chapter 6

The Physiological significance of the characteristic enhancer control during the developmental phase of mammalian life from weaning until sexual maturity

In the 1950s, we were measuring thehunger-induced orienting-searching reflex activity in rats whenwe noticed thatrats in their late developmental phase of life (2 months of age)moved with unusuallyenhanced motility compared to their peers in their early post-developmental phaseof life (4 months of age).This phenomenonpointed to the enhanced catecholaminergic activity during the developmental phase of life.After carefully reading allpertinent literature I was still unable to find any reasonable explanationregardingthe mechanismof this unusual observation; itremained for some time inconceivable (Knoll 1957).The discovery of the enhancer regulation in the mammalian brain in the 1990sand our first paper demonstrating the peculiar enhancer control during the developmental phase of mammalian lifefinally clarified the responsible mechanism of this early finding(Knoll and Miklya 1995).

Figure 6.1 shows that if wemeasure the intensity of orienting-searching reflex activity of hungry rats in a new surrounding as a function of time elapsed from the last feeding, we observe the striking difference in activity between rats being in their uphill period of life (2-month-old animals) and 4-month-old rats being already in their early post-developmental phase of life.

We also observed the awakening of sexual drive, maturation of spermatozoa and the development of the penis in male CFY rats. From the strain we used in this experiment, it was exceptional to find copulatory drive manifesting in males younger than six weeks. Although the appearance of copulatory patterns usually precedes maturation of spermatozoa and a fully developed penis, the overwhelming majority of the males reached full-scale sexual activity by the completion of their 2nd month of life.

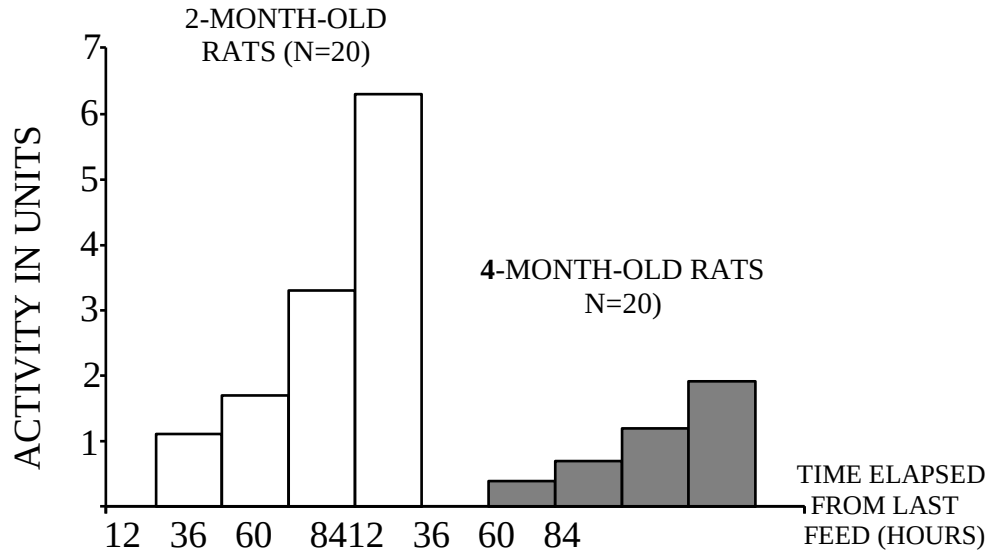

Figure6.1. Intensity of orienting-searching reflex activity of hungry rats in new surroundings as a function of time elapsed from their last feeding. Activity was measured and expressed in units from 0 to 10 (Knoll and Miklya 1995).

The interval from weaning (3rd week of life) until the end of the 2nd month of age is the decisive period for the development of a rat. During this period the rat acquires abilities crucial for survival as an instinctivemeans to ensure the survival of the species. Based on the observation that 2-month-old famished rats are significantly more active than their 4-month-old peers, we measuredtheir dopaminergic, noradrenergic and serotonergic activities in the brain before weaning (in 2-week-old rats), during the crucial developmental phase -from weaning to sexual maturity (in 4- and 8-week-old rats) - and in the early post-developmental phase of life (in 16- and 32-week-old rats). As an indicator of the basic activity of catecholaminergic and serotonergic neurons in the brain, we measured the release of dopamine (DA) from striatum, substantia nigra and tuberculum olfactorium;of norepinephrine (NE) from the locus coeruleus;and of serotonin (SE) from the raphe, in both male and female rats (Knoll and Miklya 1995).

We found that from weaning until the secondmonth of life,the rat's striatal dopaminergic system was significantly more active than either before or after that period.

Figure 6.2demonstrates a dramatic increase in the release of DA from the striatum and tuberculum olfactorium after weaning (4th week) and the return of the release of DA to the pre-weaning level (2nd week) in sexually mature rats (32nd week).

This finding explains why, as demonstrated in Figure 6.1, food-deprived rats in their developmental phase of life were significantly more mobile in an open field than their peers already in their early post-developmental phase of life. Our finding regarding the age-related changes in the dopaminergic tone in the rat brain was confirmed on Long Evans Cinnamon rats (Samuele et al. 2005).

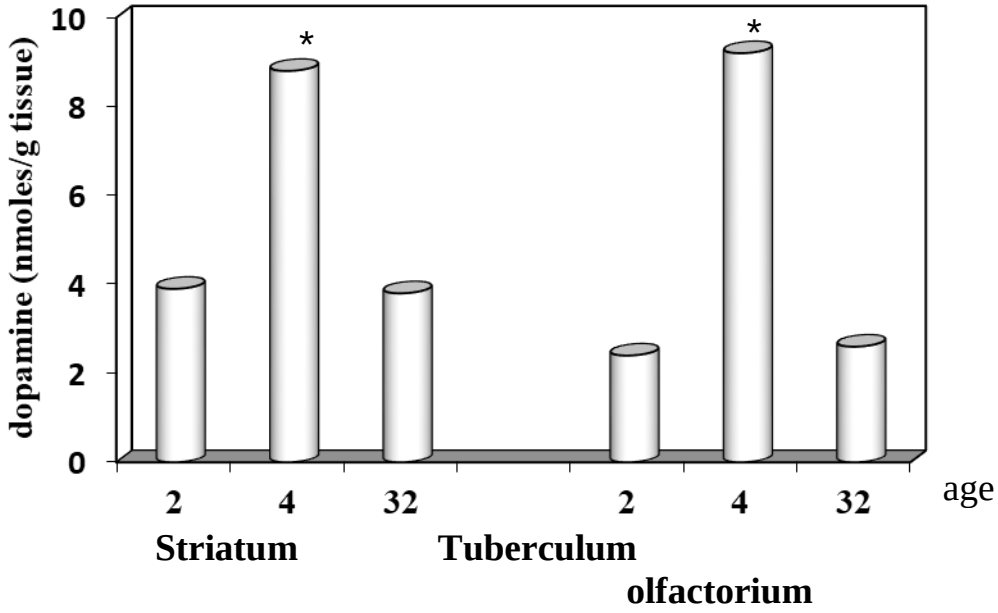

Figure 6.2. Release of DA from the striatum and tuberculum olfactorium, respectively, of male rats belonging to different age cohorts (age in weeks) N=12; *p<0.001 (Knoll and Miklya 1995).

The release of NE from the locus coeruleus (Figure 6.3) and the release of SE from the raphe (Figure 6.4) show the same dramatic increase after weaning and the return to the pre-weaning level in sexually mature rats as DA releases from the striatum and tuberculum olfactorium (Knoll and Miklya 1995).

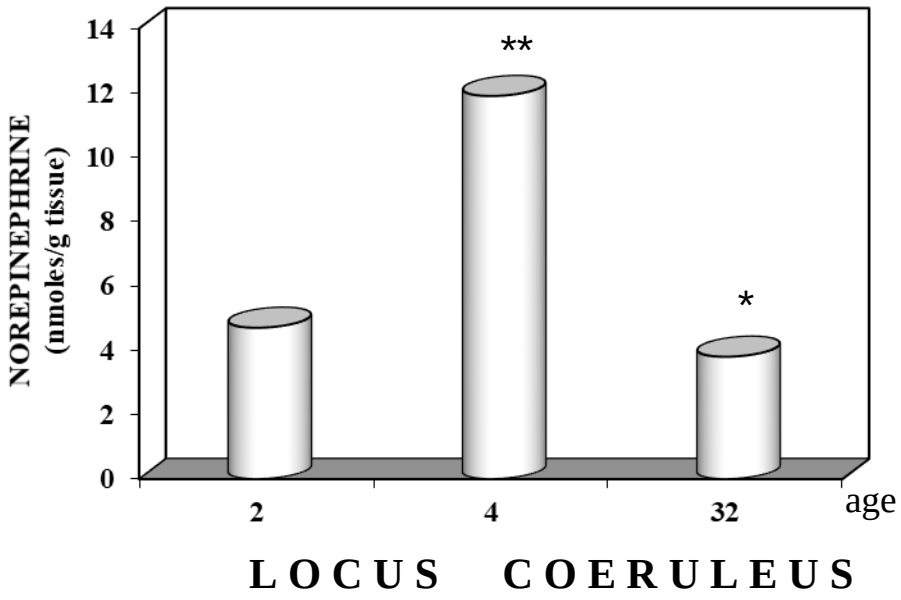

Figure 6.3. Release of NE from the locus coeruleus of male rats belonging to different age cohorts (age in weeks). N=12; *p<0.01, **p<0.001 (Knoll and Miklya 1995).

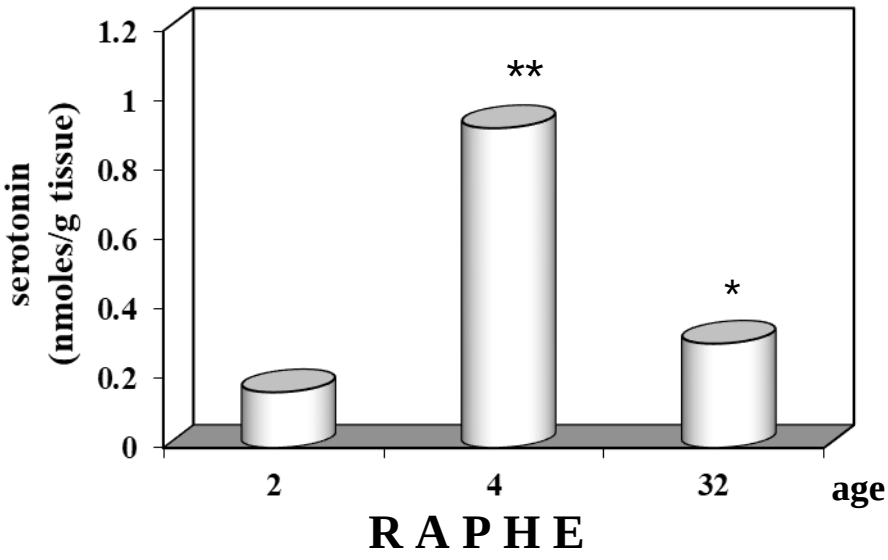

Figure 6.4. Release of SE from the raphe of male rats belonging to different age cohorts (age in weeks). N=12; *p<0.01, **p<0.001 (Knoll and Miklya 1995).

The discovery that the enhancer-regulation plays a key role in controlling the developmental period of mammalian life renders it possible to extend in the future the duration of the uphill period of life via the administration of a safe synthetic enhancer substance. This highly desirable aim is already safely realizable with a low dose DEP treatment.

From this study it was reasonable to deduce that sexual hormones play a key role in terminating the developmental phase of life.

References:

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