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

Chapter 7

The Physiological Significance of the Characteristic Enhancer Control During the Post-Developmental Phase of Mammalian Life from Sexual Maturity to Death

Since, from the discontinuation of breast feeding (end of the third week of age) until the appearance of sexual hormones (end of the second month of life),we measured in both male and female rats a significantly pronounced enhancer regulation in the dopaminergic, noradrenergic and serotonergic neurons, it was reasonable to deduce that sexual hormones play the key role in terminating the developmental phase of life (Knoll et al. 2000).

The essence ofthe post-developmental phase of life is the slow, continuous decline of brain performances, due to the enhancer-sensitive brain regulations aging.The amount of natural enhancersdecreaseand the consequences are preciselymeasurable with the continuous, progressive decline of the appropriate brain functions.

The regulation of sexual hormones starts working in rats with full capacity at the end of the second month of age. This rapid decrease in norepinephrine (NE), dopamine (DA) and serotonin (SE) from selected discrete brain regions appeared synchronously with the completion of sexual maturity. Thus, it was reasonable to assume that sexual hormones dampen the enhancer regulation in the catecholaminergic and serotonergic brain stem neurons, and this is the mechanism which terminates developmental longevity as well.

In order to qualify these observations, we castrated three-week-old male and female rats and measured the release of DA, NE and SE from selected discrete brain regions at the end of the third month of their life. We found that in male rats the amount of DA, NE and SE released from the neurons was significantly higher in castrated than in untreated or sham operated rats, signaling that sex hormones inhibit enhancer regulation in the brain (Table 7.1).

To further analyze this effect of sex hormones, we treated male and female rats subcutaneously with oil (0.1 ml/rat), testosterone (0.1 mg/rat), estrone (0.01 mg/rat) and

progesterone (0.5 mg/rat), respectively, and measured their effect on the enhancer regulation. Twenty-four hours after a single injection with the hormones, the release of NE, DA and SE was significantly inhibited in the testosterone- or estrone-treated rats (Table 7.2), but remained unchanged after progesterone treatment (Table 7.3).

In rats treated with a single hormone injection, testosterone in the male and estrone in the female was the significantly more effective inhibitor. Remarkably, the reverse order of potency was found in rats treated with daily hormone injections for 7 or 14 days (Table 7.4 and 7.5).After a two-week treatment with hormones, estrone was found in the male and testosterone in the female as the significantly more potent inhibitor of the enhancer regulation (Knoll et al. 2000).

The data prove that sex hormones terminate the hyperactive phase of life by dampening enhancer regulation in the catecholaminergic and serotonergic neurons. They initiate the transition from the developmental phase of life to post-developmental longevity, from adolescence to adulthood. This change is also simultaneously the beginning of the slow, continuous decay of the enhancer regulation in catecholaminergic and serotonergic neurons in the brain stem. As a consequence, the fixation of inextinguishable conditioned reflexes and the acquisition of drives are subject to an inevitable slowly progressing age-related decline until death.

Although the individual variation in decline of behavioral performances over time is substantial, the process developing in every brain and the decay in brain performances as well as the potential to manifestaging-related neurodegenerative diseases (Parkinson’s disease, Alzheimer’s disease) increases with the physiologically irrepressible aging of the brain. It is obvious that only the development of a safe and efficient preventive pharmacological intervention, starting immediately after the completion of sexual maturity, can significantly slow brain aging.

In our two longevity studies, performed with DEP on the robust Wistar-Logan rats, some lived beyond theirestimated maximum age of death, showing promise to findin the future efficient means to prolong human life beyond the technical lifespan. This would be a groundbreaking example of man's endeavor to outwit Nature by understanding the laws of its operation.

Table 7.1. The release of catecholamines and SE from selected discrete brain regions isolated from the brain of 3-month-old male and female rats, untreated, sham operated or castrated at the age of 3-weeks.

	Amount of biogenic amine (nmoles/g tissue) released from the tissue within 20 min				
	Dopamine			Norepinephrine	Serotonin
MALES	Striatum	Substantia nigra	Tuberculum olfactorium	Locus coeruleus	Raphe
Untreated	3.4±0.008	4.8±0.17	3.5±0.15	3.9±0.12	0.334±0.01
Sham operated	3.3±0.11	5.2±0.34	3.5±0.16	3.9±0.09	0.329±0.02
Castrated	4.4±0.17**	7.4±0.21**	4.7±0.12**	5.5±0.22**	0.921±0.02**
FEMALES					
Untreated	3.0±0.14	4.5±0.14	2.9±0.05	3.1±0.07	0.337±0.01
Sham operated	2.9±0.13	4.3±0.17	2.8±0.18	3.0±0.05	0.339±0.01
Castrated	4.6±0.29**	8.3±0.18**	3.7±0.06**	4.40±0.05**	0.491±0.03*

Paired Student's t-test. N=16. *p<0.02; **p<0.001.

Table 7.2. The release of catecholamines and SE from selected discrete brain regions isolated fromthe brain of 4-week-old male and female rats 24 hours after a single subcutaneous injection with oil (0.1 ml/rat), testosterone propionate (0.1 mg/rat) and estrone (0.01 mg/rat), respectively.

	Amount of biogenic amine (nmoles/g tissue) released from the tissue within 20 min				
	Dopamine			Norepinephrine	Serotonin
MALES	Striatum	Substantia nigra	Tuberculum olfactorium	Locus coeruleus	Raphe
Vehicle (A)	6.6±0.23	11.8±0.23	6.8±0.21	9.6±0.19	1.178±0.14
Testosterone (B)	4.7±0.19	10.8±0.34	4.8±0.13	3.4±0.21	0.581±0.11
Estrone (C)	5.8±0.21	11.6±0.26	5.8±0.20	4.2±0.35	0.918±0.04
	A:B ****	A:B *	A:B ****	A:B ****	A:B **
	A:C *	A:C ¯	A:C ***	A:C ****	A:C ¯
	B:C **	B:C ¯	B:C ***	B:C ¯	B:C *
FEMALES					
Vehicle (A)	7.7±0.27	11.8±0.26	7.9±0.17	9.0±0.26	1.120±0.07
Testosterone (B)	6.8±0.45	11.4±0.21	7.1±0.35	4.7±0.37	0.815±0.09
Estrone (C)	5.5±0.16	11.2±0.39	6.3±0.39	3.7±0.32	0.377±0.11
	A:B ¯	A:B ¯	A:B ¯	A:B ****	A:B *
	A:C ****	A:C ¯	A:C ***	A:C ****	A:C ***
	B:C ***	B:C ¯	B:C ¯	B:C ¯	B:C *

Paired Student's t-test. N=16. ¯p>0.05; *p<0.05; **p<0.02; ***p<0.01; ****p<0.001.

Table 7.3. The release of catecholamines and SE from selected discrete brain regions isolated fromthe brain of 4-week-old male and female rats, 24 hours after a single subcutaneous injection with oil (0.1 ml/rat) and progesterone (0.5 mg/rat), respectively.

	Amount of biogenic amine (nmoles/g tissue) released from the tissue within 20 min				
	Dopamine			Norepinephrine	Serotonin
MALES	Striatum	Substantia nigra	Tuberculum olfactorium	Locus coeruleus	Raphe
Vehicle	5.9±0.27	10.4±0.22	6.2±0.31	9.9±0.70	1.071±0.11
Progesterone	5.7±0.20	10.6±0.33	5.9±0.08	10.0±0.05	1.026±0.07
FEMALES					
Vehicle	5.8±0.13	10.5±0.29	6.4±0.21	10.8±0.10	1.080±0.02
Progesterone	5.8±0.15	10.1±0.30	6.2±0.22	10.4±0.80	1.470±0.03

Paired Student's t-test. N=16. p>0.05.

Table 7.4. The release of catecholamines and SE from selected discrete brain regions isolated fromthe brain of male and female rats injected once daily for 7 days subcutaneously with oil (0.1 ml/rat), testosterone propionate (0.1 mg/rat) and estrone (0.01 mg/rat), respectively.

	Amount of biogenic amine (nmoles/g tissue) released from the tissue within 20 min				
	Dopamine			Norepinephrine	Serotonin
MALES	Striatum	Substantia nigra	Tuberculum olfactorium	Locus coeruleus	Raphe
Vehicle (A)	6.2±0.24	11.9±0.37	7.1±0.18	9.5±0.20	0.914±0.04
Testosterone (B)	5.0±0.17	11.8±0.10	5.1±0.13	5.8±0.17	0.281±0.01
Estrone (C)	4.9±0.31	11.7±0.24	4.7±0.17	4.3±0.10	0.459±0.02
	A:B ***	A:B ¯	A:B ****	A:B **	A:B ***
	A:C *	A:C ¯	A:C ****	A:C ***	A:C ***
	B:C ¯	B:C ¯	B:C ¯	B:C ¯	B:C **
FEMALES					
Vehicle (A)	6.6±0.2	12.0±0.20	6.5±0.25	9.3±0.30	0.944±0.30
Testosterone (B)	3.4±0.13	10.9±0.23	4.6±0.26	5.2±0.05	0.236±0.02
Estrone (C)	5.4±0.11	10.3±0.11	5.9±0.18	5.0±0.05	0.520±0.01
	A:B ****	A:B ***	A:B ***	A:B ***	A:B ***
	A:C ***	A:C ****	A:C ¯	A:C ***	A:C ***
	B:C ****	B:C ¯	B:C ***	B:C ¯	B:C ***

Treatment started on 3-week-old rats. Brain samples were isolated 24 hours after the last injection. Paired Student's t-test. N=16. p>0.05; *p<0.05; **p<0.02; ***p<0.01; ****p<0.001.

Table 7.5. The release of catecholamines and SE from selected discrete brain regions isolated from the brain of male and female rats injected once daily for 14 days subcutaneously with oil (0.1 ml/rat), testosterone propionate (0.1 mg/rat) and estrone (0.01 mg/rat), respectively.

	Amount of biogenic amine (nmoles/g tissue) released from the tissue within 20 min				
	Dopamine			Norepinephrine	Serotonin
MALES	Striatum	Substantia nigra	Tuberculum olfactorium	Locus coeruleus	Raphe
Vehicle (A)	5.8±0.24	14.3±0.30	7.6±0.13	6.5±0.40	1.090±0.01
Testosterone (B)	6.4±0.28	13.0±0.19	5.8±0.24	5.6±0.10	0.415±0.01
Estrone (C)	4.6±0.21	9.8±0.27	5.6±0.21	2.0±0.10	0.213±0.02
	A:B ¯	A:B ***	A:B ****	A:B ¯	A:B ***
	A:C **	A:C ***	A:C ****	A:C ***	A:C ***
	B:C ***	B:C ****	B:C ¯	B:C ***	B:C **
FEMALES					
Vehicle (A)	5.1±0.06	11.7±0.13	6.2±0.15	6.7±0.25	1.007±0.01
Testosterone (B)	4.4±0.18	10.8±0.36	4.5±0.15	3.8±0.15	0.218±0.02
Estrone (C)	5.7±0.23	10.2±0.34	5.6±0.20	6.5±0.30	0.607±0.01
	A:B ***	A:B ¯	A:B ****	A:B ***	A:B ****
	A:C ¯	A:C ***	A:C *	A:C ¯	A:C ****
	B:C ***	B:C ¯	B:C ***	B:C **	B:C ***

Treatment started on 3-week-old rats. Brain samples were isolated 24 hours after the injection. Paired Student's t-test. N=16. ¯p>0.05; *p<0.05; **p<0.02; ***p<0.01; ****p<0.001.

Reference:

Knoll J, Miklya I, Knoll B, Dallo J. Sexual hormones terminate in the rat the significantly enhanced catecholaminergic/serotoninergic tone in the brain characteristic to the post-weaning period. Life Sci 2000; 67: 765-73.

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