and in the intact or castrate female[16]. Castration or testosterone treatment in the adult male rat[9] as well as castration in the female[16] does not influence the nucleus size of VMN neurons. Our findings in the male squirrel monkey shows a clear inverse relationship between the nucleus size of the VMN cells and the spermatogenic activity. In the ovariectomized female squirrel monkey kept on estrogen/progesterone replacement therapy, the average nuclear diameters of the VMN cells in 5 animals were not significantly different and were almost equal to the nucleus size of VMN cell diameter of the male with the strongest spermatogenic activity. This disagreement with the findings of DÖRNER and STAUDT[16] who found the VMN cell size in the male rat with active spermatogenesis smaller than in the female may be related to the different type of male breeding (as the rat is a continuous breeder while the squirrel monkey is a seasonally breeding animal). Another but less likely possibility is that nuclear volume changes in VMN in the female squirrel monkey were induced by the estrogen/progesterone treatment. In the female rat, changes of estrogen/progesterone levels during the estrous cycle does not influence the nuclear size of VMN cells[17].

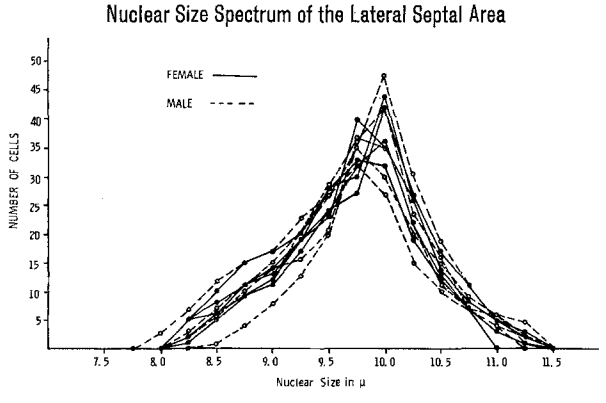

Fig. 2. Nuclear Size Spectrum of the Lateral Septal Area.

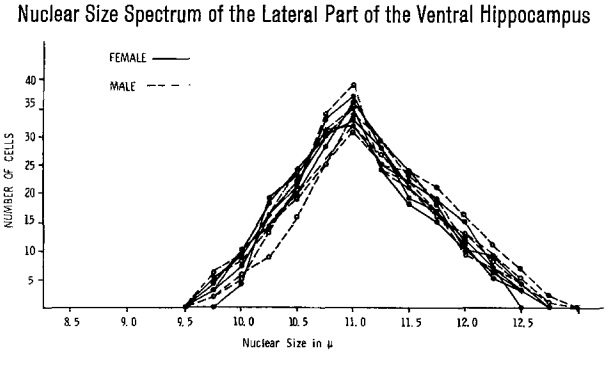

Fig. 3. Nuclear Size Spectrum of the Lateral Part of the Ventral Hippocampus.

A sex-dependent neural control of reactivity to electric footshock has been found after destruction of the VMN but not after lesions in the septum. In male rats, destruction of the VMN increases sensitivity to electric shocks but in the female no changes were found[18]. Unfortunately, as the endocrine activity of these animals was not examined, it is possible that a decrease of testosterone level increased the sensitivity to electric shock[19].

Stimulation of VMN cells induced a marked increase of activity in mitosis of spermatogonia and spermatocytes in the seminiferous tubules[7] showing that the VMN exerts some direct influence on spermatogenesis. The findings of SZENTHAGOTHAI et al.[9] that spermatogenesis persists after VMN destruction indicate that the VMN influence on testicular activity is not essential. Unilateral destruction of VMN in man has been used as a therapy in the cases of psychological deviation (exhibitionism, sex offenders, etc.) without inducing changes in either libido or spermatogenic activity[20].

The VMN area has very close connections to limbic system structures like the septum, amygdala and hippocampus[3]. Therefore, it might be possible that the limbic system which modulates the activity of the neurons that are responsible for the secretion of gonadotropin releasing hormones[6] influences the hypothalamic centers through VMN neurons with which it has direct connections[21]. Of the limbic system structures studied karyometrically, only the medial amygdala exhibits sex dimorphism[10] but not the LS or VH.

It seems probably that the VMN has a multiple role in the regulation of endocrine activity and that the different subunits of this nucleus may have different functions[17] regarding GH[1], ACTH[9] and gonadotrophic secretion[6]. We can conclude that in the squirrel monkey, a seasonally breeding animal, the nuclear size of the VMN cells exhibits changes which correlate with spermatogenic activity.

Zusammenfassung. Nachweis, dass bei ausgewachsenen Totenkopfaffen (*Saimiri sciureus*) die Zellkerndurchmesser im Nucleus ventromedialis hypothalami in der Periode der hochaktiven Spermiogenese kleiner sind als zu Beginn der Brunstperiode. Da das limbische System mit diesem Kern zusammenhängt, sind direkte Einflüsse nicht auszuschliessen.

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[16] G. DÖRNER and J. STAUDT, Neuroendocrinology *4*, 278 (1969).
[17] A. SMOLLICH, Endokrinologie *53*, 20 (1968).
[18] M. DENNIS, Expl. Neurol. *37*, 256 (1972).
[19] D. E. WOOLEY and P. S. TIMIRAS, Endocrinology *71*, 609 (1962).
[20] F. RÖDER, Med. Tribune *37*, 20 (1970).
[21] R. G. DYER and B. A. CROSS, Brain Res. *43*, 254 (1972).

Increased Cardiac Turnover of Noradrenaline after Chronic Administration of Guanethidine in the Rat

Guanethidine, which is used in the treatment of hypertension, has been shown to cause a depletion of the peripheral stores of noradrenaline[1, 2]. This drug is taken up and stored in the sympathetic ganglion nerve cells[3, 4]. However, the gross depletion of noradrenaline is not caused by a direct replacement reaction[5]. Several authors could show that chronic treatment with guanethidine caused histological damage of the adrenergic system in

Uptake of ^{3}H-(—)-noradrenaline (dpm/g) and the noradrenaline content (μg/g) in rat hearts before and after i.p. treatment with guanethidine (25 mg/kg/day)

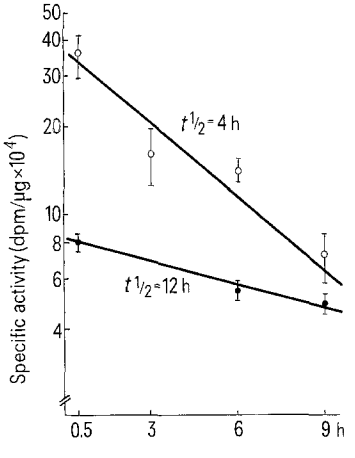
Days of treatment	Control		Guanethidine	
	^{3}H-(-7-NA) (dpm/g)	NA (μg/g)	^{3}H-(—)-NA (dpm/g)	NA (μg/g)
7	87232 ± 13444 (4)	1.00 ± 0.08 (4)	95850 ± 13028 (4)	0.24 ± 0.08 (4)
14	91808 ± 8031 (4)	1.12 ± 0.03 (4)	45842 ± 2921 (3)	0.06 ± 0.01 (3)
21	78858 ± 1860 (3)	0.90 ± 0.06 (3)	31909 ± 3520 (3)	0.10 ± 0.01 (3)

Mean values ± SEM. Number of animals in parenthesis.

adult and newborn rats[6–8]. Furthermore, guanethidine was reported to cause inhibition of uptake as well as a release of ^{3}H-noradrenaline from the heart[9]. It was therefore of interest to study the effect of chronic administration of guanethidine on the turnover of noradrenaline in the rat heart.

Materials and methods. In the experiments, male Wistar rats (TNO W.70) of about 130–160 g were used. The animals were kept under controlled conditions of light and darkness (12:12 h) with food and water ad libitum. The noradrenaline turnover in the hearts was determined in the period of light as described previously[10]: 7, 14, and 21 days after daily i.p. administration of 25 mg/kg guanethidine sulfate, the uptake of ^{3}H-(−)-noradrenaline (spec. activity 8.7 Ci/mmole; Radiochemical Centre, Amersham) by the rat hearts was determined 30 min after i.v. injection of 10 μCi/kg of the tritiated amine. Animals which had received only 0.9% NaCl i.p. served as controls. The noradrenaline (NA) content in the hearts was determined by the method of CHANG[11]. The uptake by the hearts was expressed as dpm ^{3}H-(−)-NA/g heart. The half-life of the cardiac NA was calculated by the decay of the specific activity 0.5, 3, 6, and 9 h after the injection of ^{3}H-(−)-NA.

Results. After 7 days treatment with guanethidine (25 mg/kg/day, i.p.), the uptake of ^{3}H-(−)-NA by the rat hearts was not altered 30 min after i.v. injection of the labelled NA, when compared with control animals which had received only 0.9% NaCl (Table). However, the endogenous NA content in the heart was decreased by about 75%. 14 days after the beginning of the treatment with guanethidine, the NA content was almost completely decreased to about 5% of control. At this time, the uptake of ^{3}H-(−)-NA by the hearts was diminished to about 50% of the control uptake observed in untreated animals. Finally, 3 weeks treatment with guanethidine showed no further decrease of the endogenous NA content in the hearts. The uptake of labelled NA in these hearts was reduced to about 40% of control. As can be seen from the figure, the half-life of NA ($t\,^1/_2$ = 4 h) was greatly reduced in the hearts of animals treated with guanethidine for 3 weeks. The half-life of the cardiac NA in the control animals ($t\,^1/_2$ = 12 h) was in the same range as previously described[10]. Interestingly, the turnover of the cardiac NA of the guanethidine-treated rats (0.017 μg/g/h) was about $^1/_3$ of that of the control hearts (0.057 μg/g/h), though the endogenous NA content was decreased to about 10% of the control values.



Decay of the specific activity of noradrenaline in rat heart after 3 weeks treatment with guanethidine (25 mg/kg/day). ●—●, control; ○—○, guanethidine treatment. Each point represents the mean value ± SEM from 3–5 animals.

Discussion. The gross depletion of cardiac noradrenaline caused by chronic administration of 25 mg/kg/day of guanethidine described here is in accordance with earlier findings[1,2]. It is remarkable that after 7 days treatment with the drug, the uptake of ^{3}H-(−)-NA was not inhibited 30 min after i.v. injection of labelled amine. This is in contrast to results from acute experiments, in which guanethidine (20 mg/kg) greatly inhibited the NA uptake by rat hearts, when administered 30 min before ^{3}H-noradrenaline[9]. In our chronic experiments, a decreased uptake of ^{3}H-(−)-NA by the hearts was only observed after 14 and 21 days of daily treatment. Since it was reported that prolonged administration of guanethidine in the rat caused histological damage to the adrenergic system[6–8], it can be assumed that the decreased uptake of ^{3}H-(−)-NA by the heart after 14 and 21 days of treatment with guanethidine is probably due to a partial degeneration

[1] P. A. SHORE, Pharmac. Rev. *14*, 531 (1962).
[2] L. L. IVERSEN, *The Uptake and Storage of Noradrenaline in Sympathetic Nerves* (Cambridge University Press 1967).
[3] R. KUNTZMAN, E. COSTA, G. L. GESSA and B. B. BRODIE, Life Sci. *1*, 65 (1962).
[4] G. M. BISSON and E. MUSCHOLL, Naunyn-Schmiedebergs Arch. exp. Path. Pharmak. *244*, 185 (1962).
[5] L. MAÎTRE and M. STAEHELIN, Biochem. Pharmac. *20*, 1233 (1971).
[6] J. JENSEN-HOLM and P. JUUL, Acta pharmac. tox. *28*, 283 (1970).
[7] G. BURNSTOCK, B. EVANS, B. J. GANNON, J. W. HEATH and V. JAMES, Br. J. Pharmac. *43*, 295 (1971).
[8] O. ERÄNKÖ and L. ERÄNKÖ, Histochem. J. *3*, 451 (1971).
[9] G. HERTTING, J. AXELROD and G. WHITBY, J. Pharmac. exp. Ther. *134*, 146 (1961).
[10] B. LEMMER and R. SALLER, Naunyn-Schmiedeberg's Arch. Pharmac. *278*, 107 (1973).
[11] C. C. CHANG, Int. J. Neuropharmac. *3*, 643 (1964).

of sympathetic neurons. However, the reduced half-life of cardiac noradrenaline after chronic administration of guanethidine indicates that synthesis of NA still occurred and that the organism tried to compensate for the depleted stores of the neurotransmitter, noradrenaline. These biochemical results are supported by histochemical findings. A complete depletion of NA in the sympathetic nerves of rat iris was observed after 3 weeks treatment with guanethidine (25 mg/kg/day). However, after a prolonged treatment with the same dose up to 5 weeks, a refillment in some of the sympathetic nerves in rat iris was observed 15 min after i.v. injection of 0.2 µg/kg α-methyl-noradrenaline[12].

Zusammenfassung. Chronische Behandlung mit Guanethidin führte bei Ratten neben einer starken Verminderung des endogenen Noradrenalingehaltes im Herzen zu einer ausgeprägten Verminderung der Aufnahme von ^{3}H-(−)-Noradrenalin und zu einem stark beschleunigten Noradrenalinumsatz.

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[12] H. Grobecker and B. Lemmer, in preparation.

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Aphrodisiac Effect of L-DOPA and Apomorphine in Male Sexually Sluggish Rats

In our first report on the stimulatory effect of parachlorophenylalanine (PCPA) on male sexual activity in rats, we observed that male to male mounting behavior produced by this drug was greatly potentiated by pargyline, a monoamine-oxidase inhibitor[1]. Since the administration of pargyline to animals treated with PCPA, a specific inhibitor of serotonin synthesis[2], produces a selective accumulation of brain catecholamines in the absence of serotonin, we suggested that this monoamine might inhibit and catecholamines stimulate sexual behavior in male animals[1].

The present report shows that either apomorphine, or a combination of Ro 4-4602 with L-DOPA, increases the copulatory behavior of sexually sluggish male rats, and that this effect is prevented by haloperidol. In addition, haloperidol suppresses the spontaneous copulatory behaviour of rats with high level of sexual activity. These results suggest that brain dopamine stimulates copulatory behaviour in male rats.

Male wistar rats, weighing 300–350 g, were housed individually, starting at least 1 week before the beginning of the experimental period, under a reversed light-dark cycle (with light from 21.00 h to 09.00 h) and fed ad libitum. Each rat underwent 4 mating tests with a female in oestrus, at weekly intervals, as described below. At the end of this training period, 50 of these rats which did not reach ejaculation in 3 out of 4 of the mating tests, were classified as sexually sluggish and selected for this study.

Female wistar rats were ovariectomized 3 weeks before use and brought into heat by s.c. injections of oestradiol and progesterone in olive oil[3]. Mating tests were carried out during the dark phase of the cycle, from 10.00 h to 12.00 h, in a red light.

A female was introduced into the male's own cage and the test was terminated if the male rat failed to ejaculate within 30 min. Patterns of copulatory behaviour were scored according to Beach[4]. Every animal received one mating test under each of the 6 treatments tested, according to a latin square design.

The Table shows the effect of apomorphine and a combination of L-DOPA with Ro 4-4602, a peripherally

[1] A. Tagliamonte, P. Tagliamonte, G. L. Gessa and B. B. Brodie, Science *166*, 1433 (1969).

[2] B. Koe Kenneth and A. Weissman, J. Pharm. exp. Ther. *154*, 499 (1966).

[3] B. J. Meyerson, Archs int. Pharmacodyn. *150*, 4 (1946).

[4] F. A. Beach and A. M. Holz-Tucker, J. comp. Physiol. Psychol. *42*, 433 (1948).

Stimulation by apomorphine or L-DOPA of the copulatory behaviour of male sluggish rats and inhibition of this effect by haloperidol

Treatment	Haloperidol (mg/kg i.p.)	% of animals exhibiting at least one		
		Mounting[a]	Intromission[a]	Ejaculation[a]
Saline	—	58	54	14
Apomorphine	—	80	80	62
Ro 4-4602 + L-DOPA	—	90	90	64
Saline	1	0	0	0
Apomorphine	1	20	20	12
Ro 4-4602 + L-DOPA	1	10	10	0

Each values was obtained from 50 rats. Each rat underwent different mating tests, at weekly interval, with and without treatment. Two doses of L-DOPA (100 mg/kg each) were injected i.p. 20 and 50 min after Ro 4-4602, respectively. The experiment was performed $^1/_2$ h after the last treatment. [a] Occurring within 30 min after male and female rats were paired. Apomorphine (0.5 mg/kg) and haloperidol were injected 15 min and 2 h prior to the mating test, respectively.