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A Serotonergic System Involved in the Grooming Behavior of Cats with Pontile Lesion[1]

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RANDALL, W. AND M. TRULSON. *A serotonergic system involved in the grooming behavior of cats with pontile lesions.* PHARMAC. BIOCHEM. BEHAV. 2(3) 355–360, 1974. – Cats with pontile lesions exhibit an abnormal grooming behavior that consists of a disintegration of the appetitive and consummatory components. A serotonergic system is implicated because both 5-hydroxytryptophan and seryl-trihydroxybenzyl-hydrazine (but not dihydroxyphenylalanine) abolish the abnormal behavior, and because para-chlorophenylalanine abolishes the effectiveness of seryl-trihydroxybenzyl-hydrazine. The effectiveness of 5-hydroxytryptophan is abolished in cats pretreated with both para-chlorophenylalanine and seryl-trihydroxybenzyl-hydrazine. These results indicate that 5-hydroxytryptophan must first be decarboxylated to 5-hydroxytryptamine before it has an effect on the behavior. Additional evidence that a serotonergic system is involved in the grooming behavior was obtained by determining the activity of the enzyme, tryptophan hydroxylase, in the superior colliculi of cats with unilateral pontile lesions. A decreased activity ipsilateral to the unilateral lesion was found, suggesting that a transection of serotonergic input to the superior colliculus may be a primary effect of the lesion.

Cats Pontile lesions Grooming behavior 5-hydroxytryptamine Seryl-trihydroxybenzyl-hydrazine Tryptophan hydroxylase Superior colliculus

CATS with pontile lesions exhibit an abnormal grooming behavior that consists of a tactually-induced dissociation of the consummatory and appetitive components: when any part of the pelage is touched, the consummatory behavior that is normally directed to that part occurs, and its occurrence is not preceded by the usual appetitive phase of the behavior. Thus no orientation of the grooming behavior to the body surface occurs; the behavior occurs in midair and is completely non-functional. For example, two major consummatory behaviors are used to scratch: the rostral part of the body surface is scratched by the familiar scratch reflex using the foot, and the caudal part of the body surface, where the foot cannot reach, is scratched by the grooming bite, a shallow scratching bite used by carnivores as well as other animals. When you touch the rostral part of the body surface of a cat with the pontile lesion, the scratch reflex occurs completely divorced from the normally-preceding orienting behavior, and when you touch the caudal part of the body surface, the grooming bite is emitted in midair, one discrete grooming bite for each touch with a latency of about 50 ms (complete details have been presented by Randall, [18]). The behavior has the rather unique property of waxing and waning with the seasons of the year, i.e., a cat with the pontile lesion is normal at certain times of the year and at other times exhibits the abnormal grooming behavior; the immediate outcome of the lesion, then, depends on when it is made [18, 20, 21, 24]. The lesion-induced behavior is of special interest because of the ubiquitous applicability of the appetitive-consummatory dichotomy. Sherrington [25] and Craig [5] emphasized the importance of this dichotomy, and Lorenz and Tinbergin [13], among others, have analyzed animal behavior in these terms.

Previous studies indicated that systemic injections of 5-hydroxytryptophan (5HTP) and microinjections of 5-hydroxytryptamine (5HT) into the superior colliculus abolished the abnormal grooming behavior [29]. Systemic injections of dihydroxyphenylalanine (DOPA) had no effect. One possible explanation of these findings is that a serotonergic input to the superior colliculus is transected by

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the pontile lesion. Dahlstrom and Fuxe [6] found 5HT cell bodies in the ventral-lateral tegmentum (their Locus B9), an area included in the pontile lesion, and 5HT nerve endings are found in the superior colliculi [7]. The electrical activity of single units in the cat's superior colliculi is changed with iontophoretic application of 5HT [27], 5HT is released into the medium from tissue slices of the cat's superior colliculus when the intact optic tract is electrically stimulated [10], and Gal and Patterson [8] found a higher tryptophan hydroxylase activity in tectum than hypothalamus. If the genesis of the abnormal behavior involves a transection of a serotonergic input to the superior colliculi, then two possibilities for the 5HTP action exist: (1) direct action on 5HT receptors, and (2) decarboxylation at other sites followed by diffusion to the 5HT receptors. When receptors are denervated they respond to additional substances [4] so that a direct effect of 5HTP cannot be excluded. If 5HTP has its usual effect of abolishing the abnormal behavior when decarboxylation is prevented, then denervation supersensitivity would be involved. In the present study, the decarboxylase inhibitor, seryl-trihydroxybenzyl-hydrazine, is administered to cats with pontile lesions that are exhibiting the abnormal behavior, and then the effect of 5HTP injections are determined.

Further information on denervation of a serotonergic input to the superior colliculus as a primary effect of the lesion may be obtained by determining the activity of the enzyme, tryptophan hydroxylase, in the superior colliculi after unilateral pontile lesions. If denervation is an aspect of the primary effect of the lesion, then unilateral lesions should produce differences in the contra- and ipsi-lateral superior colliculi. A result of no difference in tryptophan hydroxylase activity between the two superior colliculi after a unilateral lesion could indicate a systemically-mediated effect, which is possible in the present case because of the lesion-induced systemic changes in glucocorticoids [22] and adrenalin [23]. Glucocorticoids, for example, are known to increase the activity of tryptophan hydroxylase [1]. Thus, the second approach to the question of denervation used in the present study is an assay of tryptophan hydroxylase in the superior colliculi after unilateral pontile lesions.

METHOD

Nineteen adult male cats, caged individually in an air-conditioned room, received either unilateral or bilateral pontile lesions. These lesions were stereotaxic, anodal, and made with direct current in the usual manner and as previously described [18].

Decarboxylase Inhibition

Eleven cats with bilateral pontile lesions were used in the study of decarboxylase inhibition.The initial plan was to first block the endogenous conversion of 5HTP to 5HT with seryl-trihydroxybenzyl-hydrazine in cats with the abnormal behavior and then determine if exogenous 5HTP still retained its usual efficacy in abolishing the abnormal behavior. However, preliminary trials with 3 cats (see results) indicated that an additional pretreatment with parachlorophenylalanine (PCPA) was required. Therefore, in the main experiment, 8 cats with pontile lesions that were exhibiting the abnormalities in grooming behavior were fed PCPA (150 mg/kg body weight/day) in Gourmet cat food for 6 days, and then on the seventh day half of the cats received seryl-trihydroxybenzyl-hydrazine (one intraperitoneal injection: 200 mg/kg) and the other half received the vehicle injection (3 ml of saline). Seventy-five min later all 8 cats received 5HTP (a single injection intramuscularly, 75 mg/kg of 5-hydroxy-DL-tryptophan, obtained from Sigma). The 75-min interval between the two injections was chosen so that the peak effect of both compounds would coincide.

L-DOPA Injections

Pretreatment with PCPA could abolish the effect of seryl-trihydroxy-benzyl-hydrazine in at least 2 ways: an inhibition of tryptophan hydroxylase, its major effect, or an inhibition of catecholamine synthesis [11,28]. To determine if seryl-trihydroxybenzyl-hydrazine was abolishing the abnormal behavior by increasing systemic levels of DOPA, intramuscular injection of l-DOPA were made in three additional cats that had pontile lesions and that were exhibiting the abnormal grooming behavior. Attempts to abolish the abnormal behavior with l-DOPA (anhydrous crystals from Sigma suspended in saline plus 0.3% gum tragacanth) were made on two separate occasions, with the dosages ranging from 60 to 175 mg/kg body weight.

Tryptophan Hydroxylase Activity

Fourteen weeks after the unilateral pontile lesions, the superior colliculi ipsilateral and contralateral to the lesion were separately analyzed for tryptophan hydroxylase activity by the method of Gal and Patterson [8]: after homogenization in tris-acetate buffer, the supernatants were incubated with an excess of cofactor (2-amino-4-hydroxy-6-methyltetrahydropterin) and tryptophan. The amount of 5-hydroxyindoles produced is then determined fluorometrically after transformations with 0-phthalaldehyde. 5HT (the creatinine sulfate from Sigma) was used as the standard. The appropriate controls include an aliquot to determine the endogenous 5-hydroxyindoles, whose value is subtracted from the aliquots treated with cofactor and tryptophan. The results are expressed in terms of the protein content of the supernatant as determined spectrophotometrically by the method of Waddell [30], a method validated for brain by Murphy and Kies [15]. The amount of protein in the supernatant varied among the cats from 0.6 mg to 1.5 mg per aliquot, which is within the linear response range as determined by Gal *et al.* [8]. Five cats with unilateral pontile lesions were used in the study of tryptophan hydroxylase activity.

Measuring the Abnormal Grooming Behavior

The abnormal behavior was quantified with the use of standard outline diagrams of a cat [22]: cutaneous stimuli were directed systematically to the body surface of the cat, and those regions from which consummatory grooming fragments were elicited were plotted on the outline diagrams. The area plotted on the standard diagrams was used as a quantitative estimate of the grooming abnormality. Plots of the abnormality on the outline diagram were made once a day before and during the PCPA administration in order to verify that a stable abnormality existed. Additional plots of the abnormal grooming behavior were obtained at 1-hr intervals before and after seryl-trihydroxybenzyl-hydrazine, 5HTP and DOPA were administered. Statistical

evaluations of the drug-induced changes in the quantified grooming abnormality and in the lesion-induced change in tryptophan hydroxylase activity were made with the appropriate *t*-tests (one-tailed).

Anatomy

In the study of tryptophan hydroxylase activity, verification of the locus of the lesions was made by gross dissection and photographs of the maximum extent of the lesions were made. The brain stems of the other cats were fixed in Formalin, dehydrated in a series of alcohols and infiltrated and embedded in paraplast. Two serial transverse sections were obtained at 1/2 mm intervals and stained with cresyl violet and Heidenhain methods. Reconstruction of the lesions were made in transverse and parasagittal planes.

RESULTS

Decarboxylase Inhibition

1. First preliminary trial – effect of seryl-trihydroxybenzyl-hydrazine. When seryl-trihydroxybenzyl-hydrazine was administered to 3 cats with pontile lesions, the abnormal grooming behavior was abolished. Because 5HTP abolishes the abnormal grooming behavior when injected systemically, it was tentatively assumed that seryl-trihydroxybenzyl-hydrazine was abolishing the abnormal behavior by the same way, i.e., peripheral decarboxylase inhibition was resulting in increased systemic levels of 5HTP before central inhibition was effected. Therefore, a second preliminary trial was run in which the supposed increase in 5HTP was blocked by pretreatment with PCPA.

2. Second preliminary trial – effect of seryl-trihydroxybenzyl-hydrazine after PCPA. When the same 3 cats again exhibited the abnormal grooming behavior and were then pretreated with PCPA for 5 days, no effect of seryl-trihydroxybenzyl-hydrazine on the abnormal behavior occurred.

3. The main experiment – effect of 5HTP. When the cats with pontile lesions that were exhibiting the abnormal behavior were pretreated with both PCPA and seryl-trihydroxybenzyl-hydrazine, no change in the abnormal grooming behavior occurred when 5HTP was administered. Table 1 indicates the usual effect of 5HTP [29] of abolishing the abnormal grooming behavior in the 4 control cats and the absence of an effect of 5HTP on the cats receiving the decarboxylase inhibitor. No overlap in the scores between the 2 groups existed.

DOPA Injections

The abnormal grooming behavior was not affected by l-DOPA injections. Three cats with abnormal grooming behavior received different dosages of l-DOPA (60 to 175 mg/kg) on two different occasions, but no changes in the abnormal grooming behavior were discernable.

Tryptophan Hydroxylase Activity in the Superior Colliculi

The activity of tryptophan hydroxylase in the superior colliculus ipsilateral to the lesion was decreased significantly ($p<0.05$) with the average decrease for the 5 cats 12% (Table 2). No differences in the endogenous 5-hydroxyindoles between the two colliculi were detected. In 3 of the cats, addition of tryptophan to the incubation media without the cofactor was made and resulted in a marked increase in tryptophan hydroxylase activity both ipsi- and contra-lateral to the lesion.

TABLE 1

THE PERCENTAGE OF THE BODY SURFACE FROM WHICH CONSUMMATORY GROOMING FRAGMENTS WERE OBTAINED BEFORE AND AFTER dl-5HTP (75 mg/kg), FOLLOWING PRETREATMENT OF ALL 8 CATS WITH pCPA (150 mg/kg/day FOR 6 DAYS) AND HALF WITH SERYL-TRIHYDROXYBENZYL-HYDRAZINE (STHBH, 200 mg/kg)

		Before 5HTP*	After 5HTP			Average Difference
		0	1 hr	2 hr	3 hr	
CATS that received STHBH	271	2.6	1.3	0	0	– 2.0
	301	20.7	19.4	25.9	26.1	6.0
	310	79.6	83.0	86.5	86.2	5.1
	329	6.4	4.3	8.0	3.7	0.5
CATS that received vehicle	265	5.0	3.4	0	0	– 4.2
	269	80.0	79.8	28.5	36.6	–47.3
	273	2.7	2.8	0	0	– 2.8
	306	11.4	14.4	0	0	–12.9

*STHBH and Vehicle were administered at zero hr and 5HTP at 1¼ hr. pCPA was administered during the 6 days before zero hr. The 5HTP-effect for the difference scores for STHBH vs vehicle groups is significant ($p<0.02$).

Anatomy

The lesions were located in the same pontile region as in previous studies: the electrode tract entered the brain stem at the intercollicular level and ended in the ventral-lateral tegmentum, destroying portions of the paralemniscal and central tegmental fields. Pontile nuclei and the middle cerebellar peduncle were partly degenerated, as were the medial and lateral lemnisci. Figure 1 shows a reconstruction of a bilateral lesion from the pharmacological studies. The upper half of Fig. 1 is a parasagittal reconstruction in the plane indicated by the small arrows at the bottom of the figure. The large arrows in the middle of the figure indicates the plane of the 3 transverse reconstructions which are illustrated in the lower half of the figure. Cross-hatching indicates a complete absence of neurons, and stippling indicates a partial absence. The outer border of stippling generally represents the edge of gliosis. The unilateral lesions were found in the same area.

DISCUSSION

The unilateral decrease in tryptophan hydroxylase activity suggests that denervation is involved because a difference in activity of the enzyme between the superior colliculi ipsilateral and contralateral to the lesion cannot be attributed to systemic factors. Previous comparisons of

TABLE 2

TRYPTOPHAN HYDROXYLASE ACTIVITY OF SUPERIOR COLLICULUS (n/M OF 5-HYDROXYINDOLES PRODUCED/HR/MG PROTEIN IN TERMS OF 5-HT)

	Contralateral to Pontile Lesion			Ipsilateral to Pontile Lesion		
CAT	Endogenous	Cofactor & Tryptophan (endogenous subtracted)*	Tryptophan Only (endogenous subtracted)	Endogenous	Cofactor & Tryptophan (endogenous subtracted)*	Tryptophan Only (endogenous subtracted)
324	0.71	0.95	0.52	0.49	0.85	0.51
333	0.66	1.13	0.60	0.72	0.98	0.47
335	0.96	1.24	–	1.09	0.89	–
336	0.52	1.11	–	0.52	0.91	–
337	0.93	1.02	0.56	0.57	1.08	0.73

*The contralateral and ipsilateral activities differ significantly ($p<0.05$).

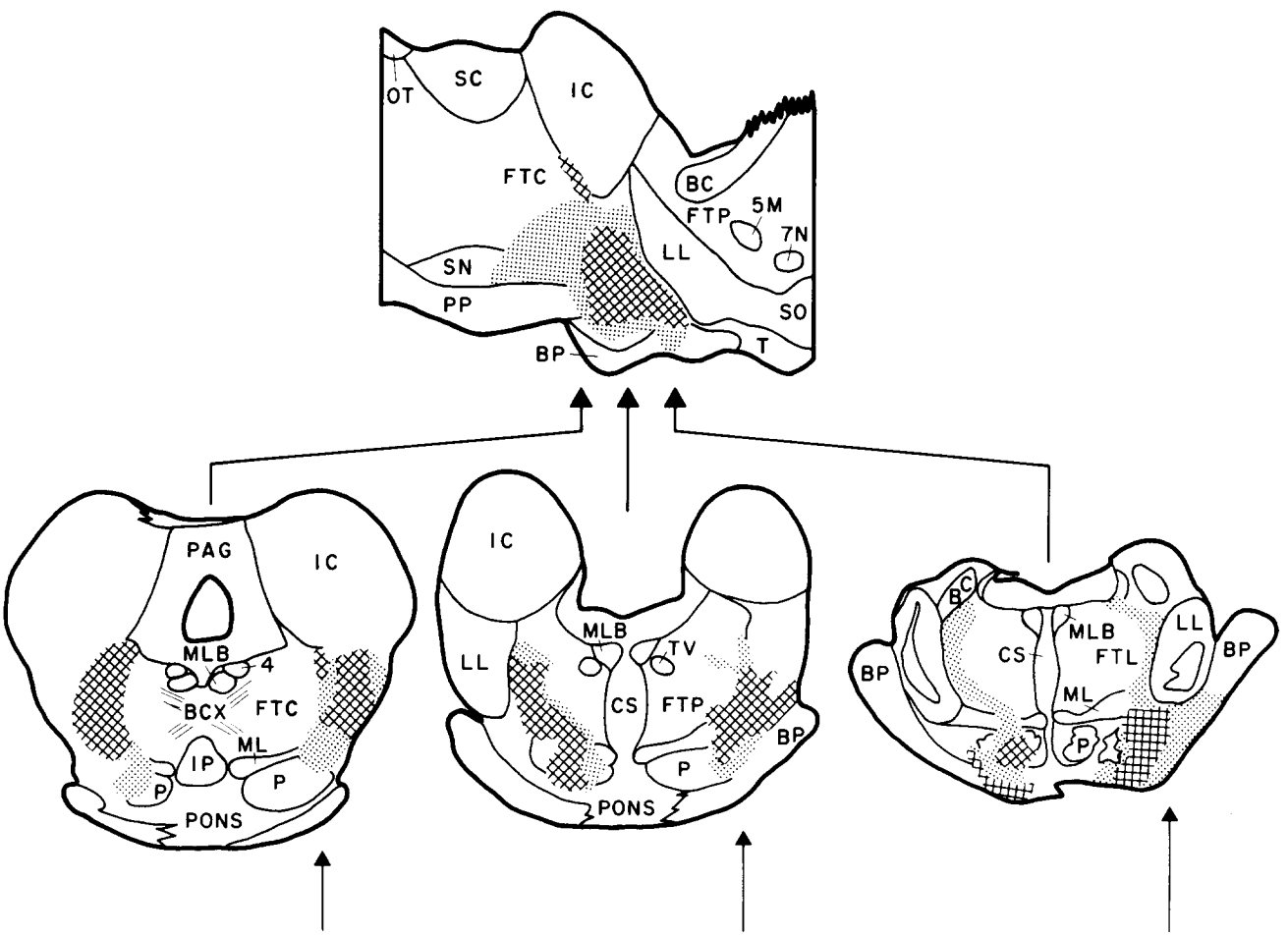

FIG. 1. The reconstruction of the pontile lesion in Cat 271, one of the cats used in the pharmacological studies. The nomeclature and abbreviations are from Berman [2]: BC, brachium conjunctivum; BCX, decussation of the brachium conjunctivum; BP, brachium pontis; CS, superior central nucleus; FTC, central tegmental field; FTL, lateral tegmental field; FTP, paralemniscal tegmental field; IC inferior colliculus; IP interpeduncular nucleus; LL, lateral lemniscus; ML, medial lemniscus; MLB, medial longitudinal bundle; OT, optic tract; P, pyramidal tract; PAG, periaqueductal grey, PP, pes pedunculi; SC, superior colliculus; SN, substantia nigra; SO, superior olive; T, nucleus of the trapezoid body; TV, ventral tegmental nucleus; 4, trochlear nucleus; 5M, motor trigeminal nucleus; 7N, facial nerve.

tryptophan hydroxylase activity in the superior colliculus were made between normal cats and cats with bilateral pontile lesions, and there was an average reduction of 35% in the group with the lesion [29] as compared with the present result of 12%. These percentages may seem small, but no evidence is available to indicate what percentage has behavioral significance. The differences in percentage of the 2 studies may be because of bilateral projections or because a bilateral lesion provides a systemic dysfunction that combines with denervation to provide lower enzyme activity. Cats with only unilateral pontile lesions do not exhibit the abnormal behavior, a result consistent with the supposed necessity of systemic effects induced by bilateral lesions. The dysfunction in glucocorticoids induced by bilateral lesions [22] could result from influences on negative feedback sites in the brain stem, negative feedback sites which have been located near the area of the pontile lesion [14,26].

A decreased activity of tryptophan hydroxylase because of denervation is consistent with previous results indicating that tryptophan does not abolish the abnormal behavior. In normal animals systemic administration of tryptophan in large dosages increases 5HT in brain [9], but in cats with the pontile lesion tryptophan administration has no behavioral effect whereas 5HTP abolishes the abnormal behavior [29]. The tryptophan hydroxylase in the superior colliculus is activated by tryptophan in vitro (Table 2), but the result in vivo would be highly localized increases in 5HT, whereas 5HT injections into the superior colliculus (which abolishes the abnormal behavior) could spread easily to all receptor sites to have a direct effect.

That systemic increases in 5HTP as a result of peripheral decarboxylase inhibition may have affected brain before the central block of decarboxylation was complete is suggested by the studies of Fletscher and Bartholine [16]: with increasing dosages of seryl-trihydroxybenzyl-hydrazine an initial sharp increase in C^{14}-catecholamines in brain (after exogenous C^{14}-DOPA administration) is followed by a gradual decline. The initial sharp increase is attributed to peripheral decarboxylase inhibition, and the gradual decline with increasing dosages of seryl-trihydroxybenzyl-hydrazine is attributed to penetration of seryl-trihydroxybenzyl-hydrazine into brain. Following systemic 5HTP injections in cats with pontile lesions, the abnormal grooming behavior disappears in about 20 min [29] whereas the peak effect of seryl-trihydroxybenzyl-hydrazine on 5HTP levels in brain is at 2 hours [17]. Thus differences in time course between peripheral and central inhibition can account for the initial effect of seryl-trihydroxybenzyl-hydrazine. A 5HTP-effect of seryl-trihydroxybenzyl-hydrazine is indicated because the effect is blocked by pretreatment with PCPA.

The study with the decarboxylase inhibitor indicates that 5HTP must first be decarboxylated to 5HT before having its behavioral effects. The presence of l-aromatic amino-acid decarboxylase in the endothelial cells and pericytes of capillaries in the rat brain is well-established, providing a blood-brain barrier for DOPA and 5HTP [3]. However, this partial barrier is not present in cat [12] so that 5HTP readily penetrates into cat brain. A major influence of seryl-trihydroxybenzyl-hydrazine, then, appears to be an enhancement of penetration of DOPA and 5HTP into the parenchyma of brain via two processes: (1) in those species with decarboxylase in the capillary walls (e.g., rat) more systemic DOPA and 5HTP enters brain because the capillary decarboxylase is inhibited, and (2) in all species peripheral decarboxylation is inhibited so that systemic DOPA and 5HTP are available for brain. A second major influence of seryl-trihydroxybenzyl-hydrazine, apparent only with high dosages as in the present study, is an inhibition of decarboxylase in brain. Recognizing, then (1) a slower penetration of seryl-trihydroxybenzyl-hydrazine into brain as compared to peripheral tissues, and (2) the absence of a blood-brain barrier for 5HTP in the cat, the diametrically opposed actions of seryl-trihydroxybenzyl-hydrazine that were found in the present report are tentatively explained.

In summary, a serotonergic neuronal system appears to be involved in integrating appetitive and consummatory components of grooming behavior because (1) the activity of tryptophan hydroxylase is decreased in the superior colliculus, a structure previously implicated in the behavior by ablation and microinjection studies; (2) pretreatment with PCPA blocks the 5HTP-like effect of seryl-trihydroxybenzyl-hydrazine; and (3) the abolition of the abnormal grooming behavior obtained by by-passing tryptophan hydroxylase with 5HTP is blocked by the decarboxylase inhibitor. Previous work has established that systemic injections of 5HTP but not DOPA abolish the abnormal behavior, and that microinjections of 5HTP or 5HT (but not tryptophan or vehicle) into the superior colliculi abolish the abnormal behavior, and that PCPA (and not alpha-methyl-tyrosine) induces the abnormal behavior in (1) cats with pontile lesions that are normal because of the time of the year [29] and in (2) adrenalectomized cats [19].

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