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Abnormalities in Grooming Behavior and Tryptophan Hydroxylase Activity in the Superior Colliculi in Cats with Pontile and Frontal Neocortical Lesions[1]

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TRULSON, M., J. NICOLAY AND W. RANDALL. *Abnormalities in grooming behavior and tryptophan hydroxylase activity in the superior colliculi in cats with pontile and frontal neocortical lesions.* PHARMAC. BIOCHEM. BEHAV. 3(1) 87–94, 1975. – Cats with pontile or frontal neocortical lesions display a dissociation of the appetitive and consummatory components of grooming behavior when their body surface is tactually stimulated, an abnormal behavior that waxes and wanes with the seasons of the year. Tryptophan hydroxylase activity is significantly decreased in the superior colliculi of cats with pontile lesions and of cats with frontal neocortical lesions. The results suggest that the change in tryptophan hydroxylase activity is mediated neuronally and is a transneuronal effect on the serotonergic input to the superior colliculi. Pharmacological manipulations of the serotonergic system in normal cats failed to induce the abnormal behavior, indicating that other factors are involved in the genesis of the abnormal behavior.

Cats Superior colliculi Lesions Grooming behavior Tryptophan hydroxylase Transneuronal Serotonin

PREVIOUS studies have implicated a serotonergic neuronal system in the grooming behavior of cats with pontile lesions [34, 36, 44, 45, 46]. These cats display a dissociation of the appetitive and consummatory components of grooming behavior when their body surfaces are tactually stimulated: immediately after tactile stimulation a consummatory grooming response appears (either a scratch, lick or grooming bite) in the absence of the normally-preceding orienting (appetitive) behavior. Since the consummatory grooming responses are not directed to the body surface, they are emitted in mid-air and are therefore completely nonfunctional (complete details of the abnormal grooming behavior are presented in Randall [33]). Dogs and cats with frontal neocortical lesions also display these grooming fragments when their body surfaces are tactically stimulated, as first described by Goltz [19] in a dog and later by Schaltenbrand and Cobb [39], Bard and Rioch [3], and Bradford [7] for cats.

The dissociated grooming behavior provides an excellent model for studying the biological bases of the classical appetitive-consummatory behavioral dichotomy of Sherrington [40] and Craig [10]. Grooming is a behavior readily amenable to laboratory studies and is of frequent occurrence, occupying 40% of the awake time of rats [6] and 67% of the nonsleeping, nonresting time of cats [44]. The normal grooming behavior is homeostatic in function as it maintains the requisite boundary for homeostatic regulation, Cannon's [9] "surface coat of non-living stuff" that separates two radically different environments. Furthermore, research on the abnormal behavior may be facilitated because the abnormal behavior varies quantitatively with the sessions of the year [33, 35, 38]; thus each cat may serve as his own control.

Microinjection of 5-HTP or 5-HT into the superior colliculi abolishes the abnormal grooming behavior for several minutes to hours, both in cats with pontile [46] and

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frontal neocortical lesions [15]. Both lesions may affect the serotonergic input to the superior colliculi, where 5-HT nerve terminals [16] and high tryptophan hydroxylase activity [17] are found. Randall and Trulson [36] provided evidence for a denervation hypothesis in the case of cats with pontile lesions: measurements of tryptophan hydroxylase activity in the superior colliculi of cats with unilateral pontile lesions revealed that the enzyme activity was significantly lower on the side ipsilateral to the lesion as compared to the contralateral side. Cats with unilateral pontile lesions, however, do not display the abnormal behavior. Therefore, in the present study tryptophan hydroxylase activity was measured in the superior colliculi of cats which display the abnormal behavior, i.e., in cats with bilateral pontile lesions and in cats with bilateral frontal neocortical lesions. Three other brain areas, thalamus, hypothalamus and neocortex, were assayed for tryptophan hydroxylase activity in order to determine if the change was confined to the superior colliculi. The hypothesis tested, then, is that there is a change in a serotonergic system in the superior colliculi (but not other brain areas) in both groups of cats that display the abnormal grooming behavior.

While 5-HT administration abolishes the abnormal grooming behavior in cats with pontile or frontal neocortical lesions, previous attempts to induce the abnormal grooming behavior in normal cats by blocking 5-HT synthesis with p-chlorophenylalanine (PCPA) have failed [34,46]. However, administration of PCPA to adrenalectomized cats induces the same kind of abnormal grooming behavior that is found in cats with pontile or frontal neocortical lesions [34]. Adrenalectomy may result in depletion of any 5-HT that would remain after PCPA administration, and because only a very small amount of 5-HT may be necessary for function [41], it is possible that a critical residuum of functional activity remains after PCPA treatment. Therefore in the present study further attempts to induce the abnormal behavior in normal cats were made, using combinations of pharmacological manipulations to deplete 5-HT and interfere with 5-HT synthesis.

METHOD

Twenty-six adult, male cats (*Felis catus L.*), housed individually in an air-conditioned room (22 ± 1°C), were used.

Surgical Procedures

The cats were anesthetized by intraperitoneal injections of sodium pentobarbital (35 mg/kg) and administered 3,3-methylethylglutaramide (20 mg/kg) to counteract the anesthetic at the completion of surgery.

Three cats received stereotaxic, anodal pontile lesions bilaterally in the usual manner and as previously described [33]. Three cats received bilateral lesions of the frontal neocortex: the neocortex rostral to the ansate and anterior ectosylvian sulcus and dorsal to the rhinal fissure was removed by aspiration. Six cats received sham surgery: the surgical procedures were terminated when the dura was exposed.

Tryptophan Hydroxylase Activity

Six to twelve weeks after surgery four different brain areas, superior colliculi, dorsal thalamus, hypothalamus, and cerebral neocortex, from the six control cats and the six cats with lesions, were assayed for tryptophan hydroxylase activity, using the method of Gal and Patterson [17]. Statistical analyses of lesion-induced changes in tryptophan hydroxylase activity were performed using the Randomization test for independent samples.

The brains were dissected as indicated in Fig. 1: a cut was made in the midline sagittal plane immediately rostral to the superior colliculi, through the corpus callosum and thalamus, and the cerebral hemispheres were spread apart, exposing the superior colliculi. The pineal was discarded. To remove the superior colliculi, four cuts were made in dorsal-ventral planes, one each on the four borders of the superior colliculi, and a fifth cut was made in a horizontal plane, immediately dorsal to the cerebral aqueduct. To obtain the dorsal thalamic tissue, four cuts were made in medial-lateral planes on the midsagittal surface of the thalamus and a fifth cut was made in a parasagittal plane approximately 3 mm from the midline, thus freeing a roughly cube-shaped tissue block. Approaching the hypothalamus ventrally, cuts in dorsal-ventral planes were made immediately caudal to the optic chiasma, immediately caudal to the mammillary bodies, and one each approximately 1 mm medial to the right and left cerebral peduncles (Fig. 1a). The tissue sample was then removed, and a 1 mm section was trimmed from the dorsal side of the hypothalamus, thus eliminating any thalamus attached to the sample. The cerebral neocortical samples were approximately 2 mm thick and contained some white matter. In cats with pontile lesions and in control cats the neocortical tissue sample consisted of large portions of the sigmoid and frontal gyri (Fig. 1b). In cats with frontal neocortical lesions, the tissue sample was taken from the lateral gyrus immediately caudal to the lesion (Fig. 1c). In all cases bilaterally symmetrical left and right tissue samples were obtained and homogenized together for the tryptophan hydroxylase assay.

Because high values of tryptophan hydroxylase activity were obtained from the dorsal thalamic tissue, an additional study of the tryptophan hydroxylase activity of this tissue was done with three control cats. Special care was taken to exclude everything but dorsal thalamus: the brain stem was sectioned in the midsagittal plane and a small piece of tissue was taken from the center of the dorsal thalamus on left and right sides. The tissue sample probably was confined to midline, medial and intralaminar nuclei and was small enough so that it was apparent that the adjacent remaining tissue was dorsal thalamus. Thus tissue samples approximately half the size of the dorsal thalamic tissue samples in the other three groups of cats were removed and assayed for tryptophan hydroxylase activity.

Pharmacological Manipulations

Four different pharmacological manipulations were performed on 14 normal cats in an effort to induce consummatory grooming fragments.

(1) Three normal cats received intraperitoneal injections of PCPA methyl ester (120 mg PCPA equivalent/kg/day) in physiological saline for several days (5 days in 1 cat and 10 days in 2 cats) followed by a single intraperitoneal injection of seryl-trihydroxybenzyl-hydrazine (200 mg/kg) in physiological saline. Thus both tryptophan hydroxylase [47] and 1-aromatic amino acid decarbyxoylas [30] were inhibited.

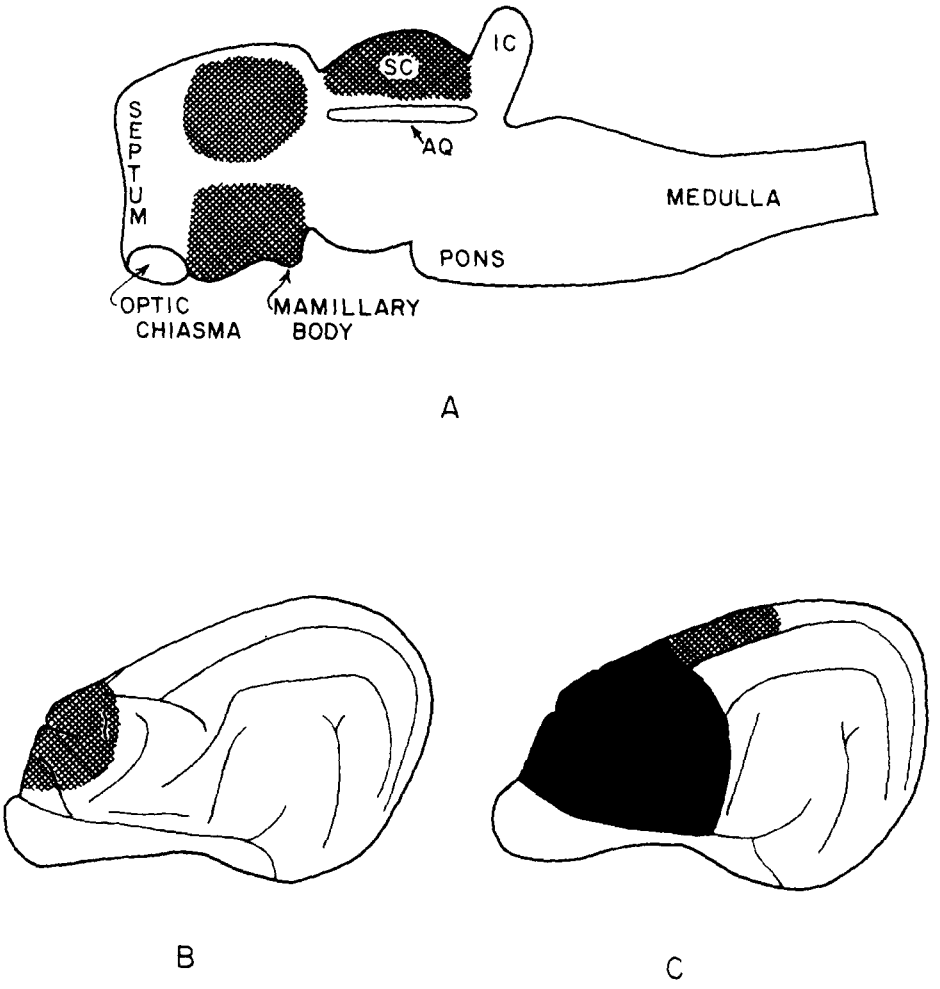

FIG. 1. Brain dissection for tryptophan hydroxylase assay and the frontal neocortical lesion. Cross-hatching indicates tissue samples used in the assay. All tissue samples were obtained bilaterally. A. Diagramatic sagittal section of the cat brain stem, showing the locations of three of the tissues used in the main study of tryptophan hydroxylase assays. The abbreviations and nomenclature are Berman's [4]: AQ, aqueduct; IC, inferior colliculus; SC, superior colliculus. B. Lateral aspect of cat brain, showing the frontal neocortical tissue sample taken from control cats and cats with pontile lesions. C. Lateral aspect of cat brain, showing the area of the frontal neocortical lesion and the neocortical tissue sample assayed in cats with these lesions.

(2) Three normal cats received PCPA (150 mg/kg/day) in gourmet cat food for nine consecutive days followed by a single intraperitoneal injection of dl-DOPA (30 mg/kg, in 0.3% gum tragacanth in physiological saline). DOPA decreases the amount of 5-HT by competing with 5-HTP for the decarboxylase [5].

(3) Three normal cats received a single subcutaneous injection of a monoamine releaser (2-hydroxy-2-ethyl-3-isobutyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11bH-benzo (a) quinolizine.) (10 mg/kg) in physiological saline [31] followed 45 min later by a single intraperitoneal injection of seryl-trihydroxybenzyl-hydrazine (200 mg/kg) in physiological saline.

(4) Four normal cats received a single intramuscular injection of reserpine (0.1 mg/kg) followed 18 hr later by a single intraperitoneal injection of dl-DOPA (30 mg/kg, in 0.3% gum tragacanth in physiological saline). McGeer, McGeer and Wada [24] found that this treatment completely depleted 5-HT in the tectum of a cat.

Measurement of the Abnormal Behavior

The identification of consummatory grooming fragments is based on four criteria: (1) the topography of the responses (biting, licking, scratching) matches that of the normal grooming repertoire (discussed below); (2) the responses are not directed to the body surface, but rather occur in mid-air; (3) the response appears immediately after tactile stimulation of the body surface and terminates immediately after the stimulation is discontinued; and (4) the

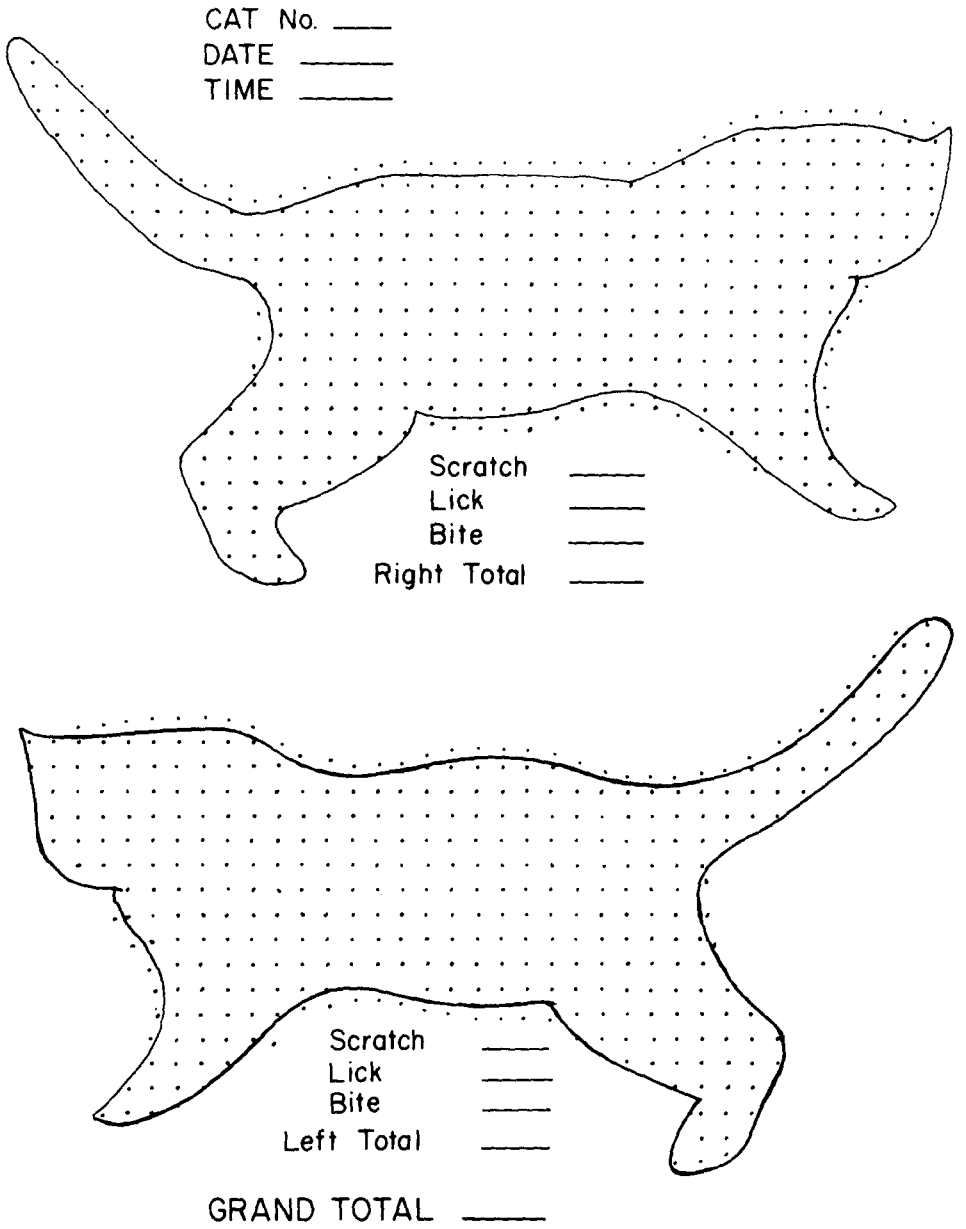

FIG. 2. Chart for the determination of the size of the responsive area. The figure displays outline drawings of right (upper) and left (lower) lateral views of a cat, onto which a grid pattern of dots has been superimposed. Since the chart is two-dimensional, the areas in the third dimension are represented by rows of dots outside the actual outline.

response can be repeatedly elicited by tactile stimulation of a given area of the body surface. The locus and size of the area of the body surface from which grooming fragments can be elicited (the responsive area) varies considerably. A quantitative measure of the responsive area was obtained using standard diagrams of the right and left lateral views of a cat containing a grid pattern of dots (Fig. 2). Imitation bites (sharply tapping the body surface), licks (gently moving a finger along the body surface), and scratches (actually scratching the body surface) were systematically directed to the cat's entire body surface, and the areas from which each type of consummatory grooming fragment could be elicited were entered on the diagram. The percentage of the body surface from which consummatory grooming fragments could be elicited was calculated by computing the fraction of the total number of dots enclosed within the responsive areas and then multiplying this number by 100. These quantitative measures were obtained before and after the pharmacological treatments of the normal cats and on the day the cats of the lesion study were killed for the tryptophan hydroxylase assay.

RESULTS

Behavior

The consummatory grooming fragments were quali-

TABLE 1

TRYPTOPHAN HYDROXYLASE ACTIVITY IN FOUR BRAIN REGIONS AND EXTENT OF RESPONSIVE AREA IN CATS WITH PONTILE LESIONS, CATS WITH FRONTAL NEOCORTICAL LESIONS, AND CONTROL CATS

	Tryptophan Hydroxylase Activity (nmoles/hr/mg Protein, Mean ± S.E.M.)				Responsive Area (% Body Surface, Mean ± S.E.M.)
	Superior Colliculi	Thalamus	Hypothalamus	Cerebral Neocortex	
Control cats	1.27 ± 0.36	1.11 ± 0.24	0.94 ± 0.09	0.31 ± 0.07	0
Cats with pontile lesions	0.69* ± 0.10	0.56* ± 0.13	0.82 ± 0.18	0.42 ± 0.03	8 ± 6
Cats with frontal neocortical lesions	0.67* ± 0.15	0.88 ± 0.27	0.71 ± 0.31	0.42 ± 0.10	55 ± 25

*Significant change from control ($p = 0.05$. Randomization test for independent samples, one-tailed test).

tatively identical in the cats with pontile and frontal neocortical lesions, and all three types of consummatory grooming fragments (bites, licks, and scratches) were observed in each group of cats.

Tryptophan Hydroxylase Activity

The activity of tryptophan hydroxylase in the superior colliculi of cats with pontile and frontal neocortical lesions was decreased 46% and 47%, respectively, as compared to control values (Table 1). The only other statistically significant change in tryptophan hydroxylase activity was found in the thalamus of cats with pontile lesions, which showed a 50% decrease.

The additional study on the center of the dorsal thalamus from three normal cats detected high tryptophan hydroxylase activity, 2.03 ± 0.23 nmoles/hr/mg protein. The initial control value for dorsal thalamus was significantly lower (1.11 ± 0.24).

Anatomy

Gross examination of the brain stems revealed that the pontile lesions were located at the level of the paralemniscal and caudal central tegmental fields, extending from the lateral tegmentum to the edge of the brain stem and into the pons, and thus similar to our previous pontile lesions. The exact location of the pontile lesion that induces the abnormal grooming behavior has been determined by histological studies [33, 35, 36, 46].

Gross examination of the frontal neocortical lesions indicated that the neocortex rostral to the ansate and anterior ectosylvian sulci was removed.

Pharmacological Manipulations

None of the 14 normal cats ever displayed any of the abnormal grooming behavior, neither before, during, nor after the pharmacological treatments.

DISCUSSION

Because the pontile and frontal neocortical lesions result in qualitatively identical behavioral abnormalities and a decrease in tryptophan hydroxylase activity in the superior colliculi (Table 1), some important anatomical link must exist. Although anatomical similarities in the outcome of frontal neocortical and pontile lesions occur (e.g., cortico-reticulo-spinal and cerebellar systems are interrupted by both lesions [8, 21, 26], and both lesions partially denervate the superior colliculi [22, 26, 42]), no information is currently available on the critical anatomical relations. The fact that the tryptophan hydroxylase defect is confined to the superior colliculi after frontal neocortical lesions indicates that an anatomical link is involved rather than a systemically mediated effect of the lesion. Previous evidence for a nonsystemically mediated effect of the pontile lesion was obtained by finding decreased tryptophan hydroxylase activity in the superior colliculi ipsilateral to unilateral pontile lesions [36].

In the present study a significant difference in tryptophan hydroxylase activity in the thalamus of control cats and cats with pontile lesions was detected (Table 1), but this significant outcome was one in six tests where no prediction of direction of change was possible. The chance of having at least one significant outcome in such a situation is greater than 0.2 [20]. Another possible source of error is the fact that the activity of tryptophan hydroxylase was significantly higher in the center tissue of dorsal thalamus as compared to the total dorsal thalamic tissue, thus indicating a restricted locus for the serotonergic neurons of this structure. If the distribution of tryptophan hydroxylase is confined to one part of the dorsal thalamus, then the level of activity of the enzyme would depend on the total amount of tissue that was selected (the larger the tissue sample, the lower the value per mg) as well as on the precise boundaries of the cut (the tissue may or may not include the site of tryptophan hydroxylase activity). While serotonergic neurons have not been observed in the dorsal thalamus, several studies have reported high tryptophan hydroxylase activity in this region [17, 27, 37]. However, in some studies it is uncertain what tissue thalamus contains; fragments of caudate, epithalamus, septum, or hypothalamus could be the source of the tryptophan hydroxylase. In the present study, careful dissection revealed that none of these other tissues were included in the dorsal thalamic tissue, neither in the initial study nor in the special study with the center piece of dorsal thalamus.

Therefore, it appears that a local region of high tryptophan hydroxylase activity exists in the dorsal thalamus.

Although the existence of a serotonergic system in the superior colliculus is well-established (reviewed in 36), the similar defect in tryptophan hydroxylase activity in the superior colliculi after pontile and frontal neocortical lesions cannot be explained in terms of the interruption of direct projections of serotonergic neurons. Even though the histochemical evidence for the cat is relatively sparse [29], there are no indications of serotonergic cell bodies other than those in and around the raphe nuclei, and no serotonergic cell bodies or fibers of passage have been found in the neocortex of any species. With regard to the pontile lesion, a small number of 5-HT cell bodies have been described in the lateral tegmentum of the rat [11]; but inspection of the reconstructions of a series of pontile lesions indicates that if these neurons are present in the cat, they would not be destroyed in every case by the pontile lesion. Thus the most parsimonious explanation of the lesion-induced abnormal grooming behavior may be that the frontal neocortical and pontile regions exert some kind of facilitory effect on that part of the serotonergic raphe system which projects to the superior colliculus, and the loss of this effect or some sequelae of the loss interacts with the glucocorticoid defect to produce the behavioral change. The change in the serotonergic neurons of the superior colliculi is probably effected transneuronally, as no serotonergic paths from the pontile or neocortical regions to the superior colliculi are known.

The tryptophan hydroxylase deficit (Table 1) is an essential but not a sufficient condition for the lesion-induced modification of grooming behavior: microinjections of 5-HT (but not noradrenalin, gamma-amino-butyric acid, tryptophan or vehicle) into the superior colliculus (but not other sites) abolish the abnormal behavior [15,46], but attempts to induce the abnormal behavior in normal cats by depleting or interfering with the synthesis of 5-HT systemically or by microinjections of PCPA locally into the superior colliculus [46] have failed. Administration of PCPA to cats with pontile lesions that are not displaying the abnormal grooming behavior (because of spontaneous seasonal reversions [33, 35, 38]) does induce grooming fragments [46]. Thus no question of the efficacy of PCPA in inducing the abnormal behavior exists in the case of cats with pontile lesions. PCPA also induces the abnormal grooming state when administered to adrenalectomized cats [34]. The glucocorticoids are further implicated in the abnormal grooming state by an inverse relationship between glucocorticoid excretion and size of responsive area found in a longitudinal study [35] and by the fact that administration of exogenous glucocorticoids abolishes grooming fragments [44,45].

Each of the four combinations of pharmacological treatments used in the present study produces a large decrease in cerebtal 5-HT, yet does not induce the abnormal grooming state. Zitrin, Beach, Barchas, and Dement [47] found that midbrain 5-HT in the cat was reduced 90 -97% after 8 consecutive days of PCPA administration at the dosage used in the present study, and the administration of the second drug (seryl-trihydroxybenzyl-hydrazine or DOPA) after PCPA treatment would decrease 5-HT levels even further. The benzoquinolizine monoamine releaser, as used in the present study, produces a 70% reduction in cerebral 5-HT [31], and addition of the decarboxylase inhibitor would result in further depletion of 5-HT. Although the dosage of seryl-trihydroxybenzyl-hydrazine used (200 mg/kg) was relatively low, Randall and Trulson [36] have demonstrated significant CNS effects in the cat using this dosage of the decarboxylase inhibitor. The reserpine plus DOPA treatment used in the present study has been shown to completely deplete 5-HT in the tectum of a cat [24]. Since the tryptophan hydroxylase data (Table 1) indicate that only a 46% reduction in the serotonergic systems in the superior colliculi is required in order for grooming fragments to develop, and because PCPA is effective in adrenalectomized cats and in cats with pontile lesions that are not displaying grooming fragments because of the time of year, two critical factors (deficits in 5-HT and glucocorticoids) are involved in the mechanism producing the abnormal grooming behavior. And because adrenalectomy by itself does not induce the abnormal grooming behavior [34, 35, 44], the pontile and frontal neocortical lesions are producing two deficits independently, i.e., the tryptophan hydroxylase defect is not a sequela of the glucocorticoid defect (and *vice versa*). Furthermore, preliminary data indicate that adrenalectomy has no effect on the activity of tryptophan hydroxylase in the cat [44]. The state of serotonergic neurons following adrenalectomy is controversial, with different studies reporting increases [13,32], decreases [1, 2, 14, 28] and no changes [12, 18, 23, 25, 43].

Previous studies of the behavioral abnormality in cats with frontal neocortical lesions reported elicitable biting or licking movements [3, 7, 39]. The classification of the movements as fragments of grooming behavior is based mainly on topographical criteria. For example, the elicited bite is a shallow scratching bite with the incisors and the canines and has the same frequency as the bite that is used by normal cats to groom. The premolars and molars are used in eating. The other kinds of bites, the killing bite, the prey-carrying bite, the sex bite, the kitten-carrying bite, all differ in frequency from the grooming bite and are not shallow bites confined to the surface. Cats are social groomers and will groom humans who are their social companions; the bite that is elicited by tactile stimulation of cats with pontile or frontal neocortical lesions feels like the social grooming that is directed to your skin by a normal cat. Not only is the elicited bite a groming behavior, but the other elicitable behaviors (licking and scratching) also match the topography of normal consummatory grooming behaviors, and the type of response elicited is a response that is normally used to groom the region of the body surface that is tactually stimulated. Thus the identity in topography of the elicited behaviors with the normal consummatory grooming behaviors indicates that the lesion-induced abnormalities are grooming fragments. An additional indication of the nature of the behavior is obtained when the tactile stimulation is continued for many seconds: although the initial elicited consummatory fragments occur in the air, i.e., completely without an orienting component, when the stimulation continues the cat may direct the consummatory response to this body surface and begin functional grooming.

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