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Sleep-Waking Patterns in Cats After Administration of Fenfluramine and Other Monoaminergic Modulating Drugs[1]

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ZOLOVICK, A. J., W. C. STERN, J. PANKSEPP, J. E. JALOWIEC AND P. J. MORGANE. *Sleep-waking patterns in cats after administration of fenfluramine and other monoaminergic modulating drugs.* PHARMAC. BIOCHEM. BEHAV. 1(1) 41–46, 1973.–Fenfluramine produced a dose-dependent, biphasic effect on sleep-waking patterns in cats. At low doses (0.4 mg/kg) fenfluramine elicited an increase in total waking time and a marked reduction in REM sleep, similar to that seen after administration of amphetamine, without affecting SWS. At anorectic doses (5.0 mg/kg) fenfluramine almost completely suppressed REM sleep, reduced waking time and increased SWS, an effect similar to that seen after administration of 5-HTP, the precursor of serotonin. The fenfluramine-induced increase in SWS was facilitated by 5-HTP and blocked by LSD, a serotonin antagonist. Serotonin was significantly reduced in the neocortex, pyriform lobe, cerebellum and hindbrain at the time of the drug's peak effect on SWS suggesting that the fenfluramine-induced increase in SWS is mediated via serotonin dependent mechanisms.

Fenfluramine Biogenic amines Norepinephrine Serotonin Amphetamine Anorectic agent LSD Sleep Waking EEG REM

FENFLURAMINE, an analogue of amphetamine, produces anorexia in experimental animals and man, yet does not elicit the psychomotor stimulation of amphetamine. In contrast to the CNS stimulating properties of amphetamine, fenfluramine produces drowsiness in man [20] and sleep in cats [10,12], as well as reduces agonistic behavior in rats and cats [21]. Although fenfluramine is generally regarded as a CNS depressant [18,30], when combined with amphetamine it can either antagonize [8] or potentiate [13] various amphetamine-induced behaviors.

The neurochemical basis for the behavioral effects of fenfluramine are poorly understood. In this regard, two interpretations have been advanced: (a) fenfluramine elicits an intraneuronal release of catecholamines, thus decreasing their levels in the brain and decreasing the availability of catecholamines for synaptic action [30]; or (b) fenfluramine lowers brain serotonin by enhancing its turnover [3], which might indicate that the behavioral effects of the drug are due primarily to increased serotonergic activity [5,24]. Results from sleep experiments in cats by Jouvet and co-workers [14] indicate that slow wave sleep (SWS) is dependent upon intact and functional serotonergic systems originating in the brain stem, whereby destruction of the serotonin containing raphé neurons or inhibition of serotonin systems with parachlorophenylalanine (PCPA) leads to suppression of SWS, which in the latter case can be restored by administration 5-hydroxytryptophan (5-HTP), the immediate precursor of serotonin. Based on the results of these experiments, we sought to assess the possibility that the fenfluramine-induced increase in SWS is mediated via a serotonergic mechanism by comparing the soporific effects of the drug when given alone or in combination with 5-HTP or LSD, a serotonin antagonist [2], and correlating the drug-induced sleep effects with brain monoamine levels in cats. In addition, the effects of amphetamine, alone and in combination with fenfluramine, were examined in an attempt to assess the similarity of action of these two agents on the polygraphic measures of the vigilance states.

MATERIALS AND METHOD

Sixteen mongrel, female cats weighing 2.5–4.5 kg, were anesthetized with pentobarbital (Diabutal—15 mg/kg), supplemented with α-chloralose (30 mg/kg), and stereotaxically implanted with chronic electrodes for recording cortical EEG, neck EMG, and dorsal hippocampal, lateral geniculate and eye movement activity. Eight and sixteen-hr continuous polygraphic recordings were carried out in an electrically shielded, dimly lit, temperature controlled, sound attentuated sleep chamber (130x75x65 cm) with

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food and water available ad lib. A flexible cable was attached to a counter-weighted 15-lead slip-ring system permitting unrestrained movement. Grass models 5 and 7 polygraphs were run at 3 mm/sec and the resulting records scored in 10 sec epochs according to the sleep criteria of Sterman *et al.* [25]. EEG activity was assigned to 4 categories: (1) awake, (2) slow wave sleep (SWS) Stage 1 (characterized by cortical synchronization and spindles interspersed with brief periods of desynchronization), (3) SWS Stage 2 (continuous cortical synchronization) and (4) rapid eye movement (REM) sleep (characterized by cortical desynchronization, complete neck atonia, rapid conjugate eye movements, ponto-geniculo-occipital waves from the lateral geniculate nucleus and hippocampal theta activity). Baseline values for the various vigilance states in untreated cats were averaged from 3 or 4 8-hr recording sessions taken at least 14 days after surgery. The drugs used (*d,l*-fenfluramine hydrochloride, *d*-amphetamine sulfate, *d,l*-5-HTP and *d*-LSD) were dissolved in 0.9% sodium chloride and administered intraperitoneally at the beginning of the recording sessions. Fenfluramine was administered at two dose levels: a low dose (0.4 mg/kg), which corresponds to an equivalent human dose used to inhibit appetite [18], and a high dose (5.0 mg/kg), which is known to reduce amine levels in the brains of mice [30] and which is anorectic in cats [10]. All cats were recorded from 0800--1600 hr.

Four normal adult cats, 1 male and 3 females, were given a single dose (5.0 mg/kg) of fenfluramine (0800 hr) 2 hr before sacrifice (during peak sleep effects) in order to determine the effects of this dose on regional brain levels of serotonin (5-HT) and norepinephrine (NE). The method of sacrifice and collection of brain tissue have been reported previously [26]. Brain regions taken for analyses were: temporal cortex, occipital cortex, anterior pyriform lobe including the amygdaloid complex, posterior pyriform lobe including the hippocampus, midbrain, basal forebrain area, lateral lobe of the cerebellum and pons-medulla. Tissue levels of NE and 5-HT were assayed according to the fluorimetric method of Thompson *et al.* [27] derived from Maickel *et al.* [19].

The effects of fenfluramine, at these dose levels, on sleep-waking patterns were assessed using paired *t*-tests (two-tailed) in which the percent of time spent in waking, total SWS (SWS 1 + SWS 2) and REM sleep during the 8-hr sleep sessions were compared to the results from the same time period of the noninjected conditions. Three one-way analyses of variance were used to assess the effects of the eight drugs in Table 1 on the three vigilance states. The

TABLE 1

EFFECTS OF FENFLURAMINE AND VARIOUS MONOAMINERGIC MODULATING AGENTS ON VIGILANCE STATES OF CATS. VALUES EXPRESSED AS PERCENT OF BASELINE VALUES (MEAN ± S.E.). BASELINE VALUES REPRESENT MEAN (±S.E.) PERCENT OF 8-HR SLEEP RECORDS FROM 13 UNTREATED CONTROLS: AWAKE = 26.6(1.8); SWS = 56.1(2.0); REM SLEEP = 17.2(0.9).

Treatment	N	Awake	SWS	REM
Fenfluramine (0.4 mg/kg)	6	124.8(7.2)*,‡	100.7(4.8)	57.4(4.9)*,‡
Fenfluramine (5.0 mg/kg)	8	49.7(5.7)*,‡	143.9(3.4)†	2.6(3.4)‡
Amphetamine (0.5 mg/kg)	3	393.9(51.4)§	4.7(1.2)§	0.0(0.0)
Amphetamine (0.5 mg/kg) + Fenfluramine (5.0 mg/kg)	3	78.8(34.4)§	129.1(8.1)§	0.0(0.0)
5-HTP (30.0 mg/kg)	3	36.7(7.7)[a]	155.3(11.0)	34.2(6.3)§
5-HTP (30.0 mg/kg) + Fenfluramine (5.0 mg/kg)	3	9.1(4.7)[a]	159.5(2.9)	0.0(0.0)§
LSD (40.0 μg/kg)	3	269.5(68.2)[a]	67.7(21.2)[a]	1.4(1.9)
LSD (40.0 μg/kg) + Fenfluramine (5.0 mg/kg)	3	114.8(18.9)[a]	90.5(8.0)[a]	0.2(0.2)

* = $p<0.05$; † = $p<0.01$, correlated *t*-test of drug vs its baseline.
‡ = $p<0.01$, analysis of variance between two dose levels of fenfluramine.
§ = $p<0.01$, analysis of variance between drug vs drug + fenfluramine.
[a] = $p<0.05$, analysis of variance between drug vs drug + fenfluramine.

effects of fenfluramine on regional brain levels of NE and 5-HT were compared to corresponding brain amine levels from 16 normal cats using Student's *t*-test.

RESULTS

A single low dose (0.4 mg/kg) of fenfluramine significantly reduced REM sleep to 57% of its baseline value over the 8-hr recording session accompanied by a 27% increase in total waking time while total SWS remained unchanged (Table 1). A single high dose (5.0 mg/kg) of the drug reduced REM sleep to 3% of its baseline value while SWS was increased by 43%. Unlike the lower dose of the drug which significantly increased wakefulness, administration of the high dose resulted in a significant reduction in total waking time. Eight-hour recordings of cats taken 24 hr after administration of the drug at either dose revealed that all vigilance states had returned to baseline values without any rebound in REM sleep. An additional 2 cats given 5.0 mg/kg of the drug and recorded continuously for 24 hr failed to exhibit a rebound in REM sleep during the second (mean = 8.2% of recording) and the final 8-hr segment (mean = 16.6% of recording) of the 24-hr record.

A single dose (0.5 mg/kg) of amphetamine resulted in a highly significant increase in total waking time and complete suppression in REM sleep while SWS was reduced to 5% of its baseline value over the 8-hr recording session (Table 1). Fenfluramine (5.0 mg/kg) readily reversed the amphetamine-induced insomnia and produced a significant increase in SWS above that of amphetamine alone, with 20–30 min periods of continuous cortical synchronization. A single dose (40 μg/kg) of LSD produced similar effects on sleep patterns as amphetamine in that total waking time was significantly elevated to 269% of its baseline value while SWS and REM sleep were significantly reduced to 68% and 2% of baseline values, respectively. When LSD was given in combination with fenfluramine (5.0 mg/kg), it completely blocked the fenfluramine-induced increase in SWS. However, REM sleep remained significantly lower than baseline in both fenfluramine plus LSD and fenfluramine plus amphetamine groups. Administration of 5-HTP, the precursor of serotonin, which restores SWS in serotonin depleted cats [14], significantly increased SWS (to 155% of its baseline value) to the same extent as fenfluramine (5.0 mg/kg) when given alone (Fig. 1). Although electrographic and behavioral manifestations of SWS were indistinguishable between the two drugs, the effects of fenfluramine differed from those of 5-HTP in that REM sleep was suppressed to a greater extent by fenfluramine. Fenfluramine completely suppressed REM sleep in 5 of 8 cats over the 8-hr recording session while 5-HTP reduced REM sleep to a mean value of 34% of baseline. When fenfluramine was administered along with 5-HTP, REM sleep was completely suppressed and cortical synchronization increased to the extent that SWS occupied 97% of the total 8-hr record (Fig. 1). Although one cat initially exhibited signs of behavioral

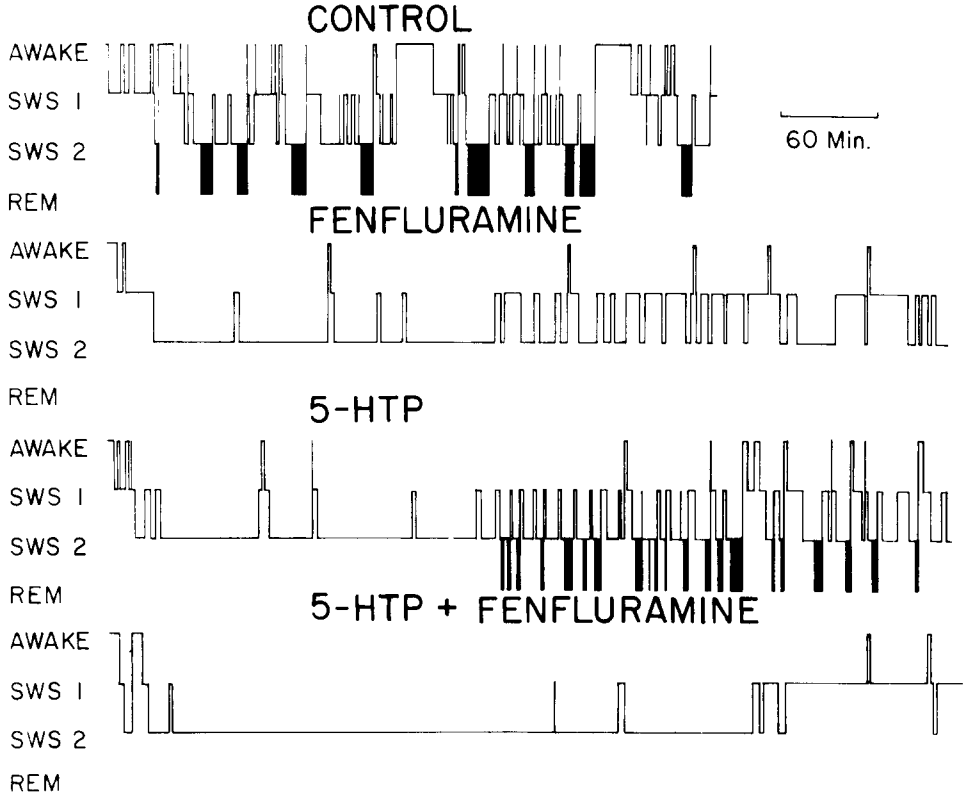

FIG. 1. Eight-hr segments from 16-hr recordings of sleep-waking patterns in representative cats immediately following intraperitoneal injection of either saline, *d,l*-fenfluramine (5.0 mg/kg), *d,l*-5-HTP(30 mg/kg) or 5-HTP (30 mg/kg) plus fenfluramine (5.0 mg/kg).

TABLE 2

EFFECTS OF FENFLURAMINE (5.0 mg/kg) ON REGIONAL BRAIN LEVELS OF SEROTONIN AND NOREPINEPHRINE. TISSUE VALUES EXPRESSED AS μG OF TISSUE (MEAN ± S.E.). CATS WERE SACRIFICED 2 HR AFTER FENFLURAMINE, IP

	Serotonin		Norepinephrine	
Brain region	Normal N = 16	Treated N = 4	Normal N = 16	Treated N = 4
Temporal cortex	0.47(0.12)	0.31(0.04)*	0.31(0.08)	0.31(0.03)
Occipital cortex	0.42(0.11)	0.27(0.02)*	0.30(0.08)	0.18(0.03)*
Anterior Pyriform lobe (amygdala)	1.47(0.38)	0.78(0.09)*	0.36(0.09)	0.25(0.02)*
Posterior Pyriform lobe (hippocampus)	1.54(0.39)	0.69(0.15)*	0.23(0.06)	0.19(0.01)
Basal Forebrain Area	1.70(0.44)	1.49(0.02)	1.19(0.31)	0.57(0.03)*
Hypothalamus	1.90(0.49)	1.28(0.03)†	1.46(0.38)	1.19(0.19)
Mesencephalon	1.35(0.35)	1.00(0.07)	0.56(0.15)	0.33(0.05)†
Cerebellum	0.38(0.10)	0.26(0.04)†	0.29(0.07)	0.27(0.04)
Pons-medulla	1.17(0.31)	0.75(0.04)*	0.37(0.10)	0.31(0.03)

* = $p<0.01$; † = $p<0.05$, two-tailed t-test

arousal and peripheral side effects (diarrhea) 20 min after administration of the two drugs, behavioral observations at half-hour intervals revealed that in all animals behavioral sleep, accompanied by cortical synchronization, persisted for 6--8 hr, which is long after the sleep effects of either drugs, when given alone, would have subsided.

Analyses of regional brain amine levels of cats killed 2 hr after administration of 5.0 mg/kg of fenfluramine, during peak effects on sleep, revealed a consistent 8--66% depletion of serotonin in all 4 animals. However, serotonin levels were not uniformly reduced throughout the brain. The greatest depletion occurred in the temporal and occipital cortex, anterior and posterior pyriform lobes and in the hindbrain while serotonin levels were reduced to a lesser extent in the cerebellum and hypothalamus (Table 2). Serotonin levels were not significantly reduced in the basal forebrain area and mesencephalon. Analysis of tissue levels of 5-hydroxy-indoleacetic acid (5-HIAA), the principal metabolite of serotonin (control; N = 4, drug; N = 4), revealed a non significant 10--38% increase in all cortical regions of the brain as well as in the hindbrain while basal ganglia structures exhibited a nonsignificant 3--14% decrease in 5-HIAA. Norepinephrine levels were significantly reduced in the latter two structures as well as in the occipital cortex and anterior pyriform lobes. Fenfluramine produced little or no change in norepinephrine in the other brain areas examined.

DISCUSSION

The results show that fenfluramine elicits a dose-dependent biphasic effect on sleep-waking patterns in cats. At low doses (0.4 mg/kg) fenfluramine was shown to possess central stimulating properties inherent in drugs of the amphetamine class, in that total waking time was significantly increased while REM sleep was significantly depressed. These data differ from those reported for the human given an equivalent dose [20] since in humans fenfluramine markedly enhanced the occurrence of drowsy sleep (SWS 1) without affecting REM sleep. However, based on anorectic efficiency, the effective dose for the cat is approximately 15 times greater [10] than for the human, indicating a differential sensitivity to this agent between the two species. The higher dose (5.0 mg/kg) used in the present study produced effects on sleep patterns consistent with results from other studies employing cats [10,12] in that REM sleep was depressed and SWS increased concomitantly. Unlike most drugs that caused a rebound in REM sleep following its suppression, withdrawal from fenfluramine failed to elicit a rebound in REM sleep in any of the cats given either dose of the drug or when fenfluramine was given chronically (5.0 mg/kg every 12 hr) for 48 hr [31].

The present results, taken together with those from previous studies [7,9], are consistent with view that the fenfluramine-induced increase in SWS is mediated *via* a serotonergic mechanism. This interpretation is supported by the parallel effect of 5-HTP on the induction and duration of SWS. While 5-HTP appears to facilitate the occurrence of SWS by enhancing synthesis [28] and utilization [24] of brain serotonin, fenfluramine appears to increase serotonergic activity by facilitating release [5,24]. The marked reduction of serotonin in neocortical, pyriform and hindbrain regions of the brain during the peak effects of fenfluramine on sleep with a concomitant nonsignificant but slight increase in its metabolite, 5-HIAA, is consistent with the above interpretation. Moreover, fenfluramine, when combined with 5-HTP, potentiated the cortical synchronizing effects of 5-HTP (i.e., increases in SWS), again suggesting enhanced activity of serotonergic mechanisms.

Administration of a high dose of LSD (40 μg/kg), an agent which decreases the central release of serotonin [15,22], blocked the fenfluramine-induced effects of sleep.

This result is in agreement with the recent findings of Jespersen and Scheel-Kruger [9] that methysergide, another serotonin antagonist, completely blocked the hypothermic effect of fenfluramine and alleviated the sedative effects of fenfluramine in dogs. Since pretreatment with ARH 3009, a potent serotonin antagonist, was effective in blocking the fenfluramine-induced increase in SWS in cats made insomniac with PCPA, a drug that depletes the brain of serotonin [16], Johnson *et al.* [12] have since questioned the role of serotonin in the mediation of the fenfluramine-induced increase in SWS. They concluded that brain levels of serotonin per se may not be related to the sedative action of fenfluramine and that the sleep effect may instead result from a direct action of the drug on tryptaminergic receptors. However, these latter results fail to exclude the possibility that a fenfluramine-induced release of serotonin is responsible for the cortical synchronization, since even chronic PCPA administration fails to completely deplete the brain of serotonin [4,16]. Thus, the possibility remains that fenfluramine may still potentiate the activity of a small remaining, but nevertheless active, pool of serotonin.

While fenfluramine has been reported to be devoid of central stimulant activity when administrated in anorectic doses [1, 17, 20], it also has been reported that fenfluramine elicits relatively weak sympathomimetic effects at subcortical (hypothalamic) and peripheral levels [6, 7, 23, 29]. The apparent discordance in reported results may, in part, be attributed to a differential sensitivity to the monoamine depleting effects of the drug within the neural substrate(s) which mediate behavioral patterns. Although data regarding regional distribution of monoamines following fenfluramine administration are lacking in most species, results from this study clearly indicate a selective depletion of serotonin within various brain regions. Serotonin concentrations were significantly reduced in neocortical, pyriform lobe and hindbrain structures, while little or no change occurred in diencephalic structures and in the midbrain. These data differ from results reported for the rat (3), in which fenfluramine was reported to elicit a preferential increase in turnover and depletion of telencephalic and diencephalic serotonin without affecting hindbrain serotonin levels. However, the time course of depletion of serotonin within various regions of the brain appears to differ in cats treated with a comparable dose (7.5 mg/kg) of fenfluramine [12]. Whereas neocortical serotonin levels were significantly reduced (40--50%) for 16 hr after administration of the drug, medullary serotonin levels returned to baseline values within 4 hr after injection. Because the small sample size used in the present study precludes a definitive conclusion regarding regional turnover of serotonin following fenfluramine, nevertheless, turnover of serotonin appeared to increase in cortical and hindbrain regions, but decreased in basal ganglia structures, i.e., mesencephalon, hypothalamus and basal forebrain areas. Whether the observed regional levels of 5-HIAA correctly reflect a real difference in the capacity of various subsystems to synthesize and metabolize serotonin at unequal rates in response to the drug or reflects only an indirect effect on clearance of 5-HIAA from regional brain areas remains to be determined. Results from the present study indicate, also, a preferential depletion of norepinephrine in limbic structures with little change in neocortical regions following fenfluramine. Although the biochemical mechanism mediating the difference in regional sensitivity to the monoamine depleting effects of fenfluramine cannot be determined from the present data, this differential sensitivity may represent the neurochemical basis underlying the apparent paradoxical behavioral effects of the drug.

In summary, the increase in SWS is consistent with the view that this agent increases postsynaptic activity in cortical synchronizing neurons by either release of serotonin [5,24] and/or by a direct action of the drug on the post-synaptic receptors [12]. Therefore, the increase in serotonergic activity combined with a decrease in available norepinephrine for synaptic action [30] might, in part, account for the depressive properties of the drug. The fenfluramine-induced decrease in REM sleep may result from an overdriving of the cortical synchronizing system to the exclusion of REM sleep rather than to direct inhibition of REM sleep generators.

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