Pharmacology Biochemistry & Behavior, Vol 24, pp 393–399, 1986 © Ankho International Inc Printed in the U S A 0091-3057/86 $3 00 + 00

Relationship of CNS Tryptaminergic Processes and the Action of LSD-Like Hallucinogens

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MARTIN, W R AND J W SLOAN *Relationship of CNS tryptaminergic processes and the action of LSD-like hallucinogens* PHARMACOL BIOCHEM BEHAV **24**(2) 393–399, 1986 —Tryptamine produces pharmacologic effects in man and the chronic spinal dog which are similar to those produced by LSD, mescaline, psilocin, DMT, DOM and DOB These effects include tachycardia, tachypnea, mydriasis, hyperreflexia, behavioral changes and in man, hallucinations Chronic spinal dogs treated chronically with LSD became tolerant to its ability to produce mydriasis, tachycardia, tachypnea and hyperreflexia, and were cross tolerant to the ability of tryptamine, psilocin, mescaline, DMT, DOM and DOB to produce these same effects Further, it was found that the brain and spinal cord contained tryptamine and could release it Further tryptamine levels were higher in the brainstem and spinal cord above the level of transection in the chronic spinal dog than in intact dogs, and the same in the spinal cord below the level of transection These observations suggested that there were both ascending and descending tryptaminergic pathways Supporting this hypothesis were the observations that L-tryptophan also produced hyperreflexia in the acute, but not the chronic, spinal dog and cat, and that L-tryptophan hyperreflexia was antagonized by α-methyldopa but not pCPA These observations and others argue that the spinal cord and brain have tryptaminergic mechanisms which are distinct from serotonergic mechanisms, and that LSD-like hallucinogens act in part through a tryptaminergic mechanism

Tryptamine LSD Psilocin Mescaline DOM DOB DMT Tolerant Spinal cord

IN the mid 1960's we began a systematic search for possible endogenous opioid ligands and ligands mediating physical dependence by looking at a variety of indolamines, phenethylamines and related compounds in the chronic spinal dog Tryptamine produced pharmacologic effects in the chronic spinal dog which resembeled those produced by LSD in man [13] These observations led to an extensive series of experiments, which will be summarized in this paper, supporting the hypothesis that tryptamine is an endogenous neurotransmitter, and that LSD-like hallucinogens exert part of their actions by functioning as "tryptaminergic" agonists More complete reviews of the mechanism of action of LSD-like hallucinogens are those of Martin and Sloan [16], Green *et al* [6] and Jones [9]

Our first experiments compared LSD and tryptamine in the chronic spinal dog Both drugs produced a similar pattern of changes including enhancement of the flexor reflex, evocation of the stepping reflex, mydriasis, increased respiratory rate and pulse rate, prolongation of the skin twitch reflex latency and an elevation of body temperature (Table 1) In addition, LSD produced some characteristic changes in behavior which included arousal, restlessness, whining, visual tracking and staring [21] (Tables 1 and 2) Other drugs which have been shown to produce LSD-like hallucinogenic activity in man including psilocin, dimethyltryptamine, mescaline and DOM (2-5 dimethoxy-4-methyl-amphetamine) produced the same pharmacologic pattern in the chronic spinal dog (Table 1) [21]

Subsequently, studies were conducted in which tryptamine was infused intravenously into man and was shown to increase blood pressure, the amplitude of the patellar reflex and pupillary diameter It also produced perceptual change and a visual hallucination in one subject [15] Some of the effects of tryptamine, because of its rapid metabolism and resulting short duration of action, may not be seen or readily produced However a sustained intravenous infusion has allowed many of its effects to become manifest in man and the spinal dog

Two other pharmacologic criteria were used to characterize tryptamine Isbell *et al* [8] and others had shown that tolerance developed rapidly to a number of LSD's effects in man and that the LSD tolerant subjects were cross tolerant to some of the effects of other LSD-like hallucinogens To further characterize tryptamine's effects it was compared with LSD in LSD tolerant chronic spinal dogs, which were made tolerant by administering LSD in a dose of 15 μg/kg subcutaneously twice daily Tolerance developed to LSD's ability to produce tachycardia, tachypnea, mydriasis,

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TABLE 1

THE EFFECTS OF SINGLE DOSES OF SEVERAL LSD-LIKE HALLUCINOGENS AND SUBSTITUTED β-PHENETHYLAMINES ON SOMATOMOTOR REFLEXES, AUTONOMIC FUNCTION AND APPETITE IN THE CHRONIC SPINAL AND INTACT DOG

	LSD	PSI	MES	DMT	T	DOM	DOB	DMA	TMA	MMDA	MDA	PEA	PMA	A
Flexor reflex	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
Stepping reflex	+	+	+	+	+	+	+	+	+	+-FR	+	+	FR	FR
Pupils	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑↑	↑↑	↑↑	↑↑	↑↑
Respiration	↑	↑	↑	↑	↑	0	↑	↑	↑	↑	↑	↑	↑	↑
Pusle rate	↑	↑	↑	↑	↑	↑	↑	↑	0	0	0	↓	↓	↓
Nictitating membrane	0	0	0	↓		0	0	0	0	↓	↓	↓	0	↓
Skin twitch (latency)	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
Temperature	↑	↑	↑	↑		↑	↑	↑	↑	↑	↑	↑	↑	↑
Appetite	0†	0†	0†			↓	↓	↓	↓	↓	↓		↓	↓
Doses (mg/kg—dog)	0 01–0 015	0 025–0 050	3 0–4 0	0 3 mg/kg/min	0 5 mg/kg/min	0 1	0 05	2 4	2 0	5 0	2 0–2 2	0 8 mg/kg/min	2 0	2 0–3 2
Dose equal to LSD (0 015 mg/kg)	0 015	0 015	3 3	0 15		0 03	0 03	1 7	1 4	4 7	1 4		2 8	2 7
Potency (dog)*	1	1 0 (0 6–1 7)	0 004 (0 0004–0 017)	0 1 (0 002–0 33)		0 5 (0 2–0 7)	0 5 (0 3–0 7)	0 009 (0 001–0 03)	0 01 (0 001–0 4)	0 003 (0 0006–0 01)	0 01 (0 001–0 4)		0 005 (0 000–0 033)	0 006 (0 0001–0 027)
Potency (man)	1	0 014	0 0003	0 003										

FR, fragmentary stepping, ↑, increase, ↓, decrease, ↑↑, marked increase, +, induces stepping reflex, 0, no effect, open spaces, no relevant data

*Potencies are expressed in mg of LSD equivalent to 1 mg of drug Relative potencies with 95% confidence limits were calculated using facilitation of the flexor reflex

†Higher doses produce some anorexia

LSD, lysergic acid diethylamide, PSI, psilocin, MES, mescaline, DMT, *N,N*-dimethyltryptamine, T, tryptamine, DOM, 4-methyl-2,5-dimethoxyamphetamine, DOB, 2,5-dimethoxy-4-bromo-amphetamine, TMA, 3,4,5-trimethoxyamphetamine, MMDA, 5-methoxy-3,4-methylenedioxyamphetamine, MDA 3,4-methylenedioxyamphetamine, PEA, β-phenethylamine, PMA, *p*-methoxyamphtamine, A amphetamine

TABLE 2

BEHAVIORAL EFFECTS IN THE CHRONIC SPINAL DOG

	LSD	PSI	MES	DMT	T	DOM	DOB	DMA	TMA	MMDA	MDA	PEA	PMA	A
Arousal	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Restlessness	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Whining	+	+	+	+		+	+	0	+	+	+	0	+	0
Tracking or staring	+	+	+	+		+	+	+	+	+	+	0	+	0
Stereotypy	0	0	0	0		0	0	+	0	0	+	+	0	+
Eye movements	0	0	0	0		0	0	0	0	0	+	+	0	+

+, behavior commonly observed 0, behavior rarely observed Blanks, observations have not been made

Abbreviations are the same as in Table 1

facilitation of the flexor reflex and to evocation of the stepping reflex Animals that were made tolerant to LSD were cross tolerant to tryptamine's ability to evoke tachypnea, mydriasis, enhancement of the flexor reflex and the stepping reflex [14] Further LSD-tolerant chronic spinal dogs were cross tolerant to many of the effects of psilocin, mescaline, DOM, DMA and DMT (Table 3)

The effects of LSD on the flexor reflex, the stepping reflex, pupillary diameter, respiration, pulse rate and skin twitch latency, which is prolonged by LSD, could be antagonized by cyproheptadine and chloropromazine Phenoxybenzamine did not antagonize these effects of LSD These same effects produced by psilocin and mescaline and tryptamine could also be antagonized by cyproheptadine and chloropromazine but not by phenoxybenzamine [13,21] These data show that LSD and tryptamine produced similar effects in the dog and man and probably have the same mechanism of action

A long series of experiments were conducted to determine if tryptamine was in the brain, whether it was released by the brain, and to further understand some of its physiologic functions Our first efforts to identify tryptamine used the spectrophotofluorometric method of Hess and Udenfriend [7] Tryptamine was identified in the brain of the

TABLE 3

TOLERANCE AND CROSS-TOLERANCE IN LSD-TOLERANT SPINAL DOG

	LSD	PSI	MES	DMT	T	DOM	DOB	DMA	TMA	MMDA	MDA	PEA	PMA	A
Flexor reflex	+	+	+	0	+	+	+	+	+	+	+	0	0	0
Stepping reflex	+	+	+	+	+	+	+	+	+		+	+		
Pupils	+	+	+	0	+	+	+	+	0	0	0	0	0	0
Respiration	+	+	+	+	+	+NS	+	+	+	0	0	0	0	0
Pulse rate	+	+	+	+	+NS	+	+	+	0			0	'	0
Temperature	+	+	0	0		+	+	+	+	0	+	0	0	0
Skin twitch	+	+	+	+		+	+	0	0	+	+	0	0	0
Behavior	+	+	+	+		+	+	+	+	0	+	0	0	0

+ tolerance or cross-tolerance in LSD-tolerant spinal dog 0, no tolerance or cross-tolerance Blanks no observations
NS, not statistically significant
Abbreviations are the same as in Table 1

TABLE 4

TRYPTAMINE BRAIN LEVELS (ng/gram ± SEM) OF SEVERAL SPECIES DETERMINED SPECTROPHOTOFLUOROMETRICALLY

Rat	20 9 ± 4 7 (15)
Guinea Pig	20 7 ± 7 9 (21)
Dog	32 1 ± 3 3 (11)
Cat	52 2 ± 6 2 (6)
Steer	83 4 ± 18 6 (8)
Man	184 9 (1)

From Sloan *et al* 1975

TABLE 5

RAT BRAIN LEVELS OF TRYPTAMINE (ng/gram ± SEM) AS DETERMINED BY THREE METHODS

Dansyl Chloride	21 1 ± 7 9
Enzymatic Isotopic	23 2 ± 3 2
Fluorometric	21 1 ± 7 9

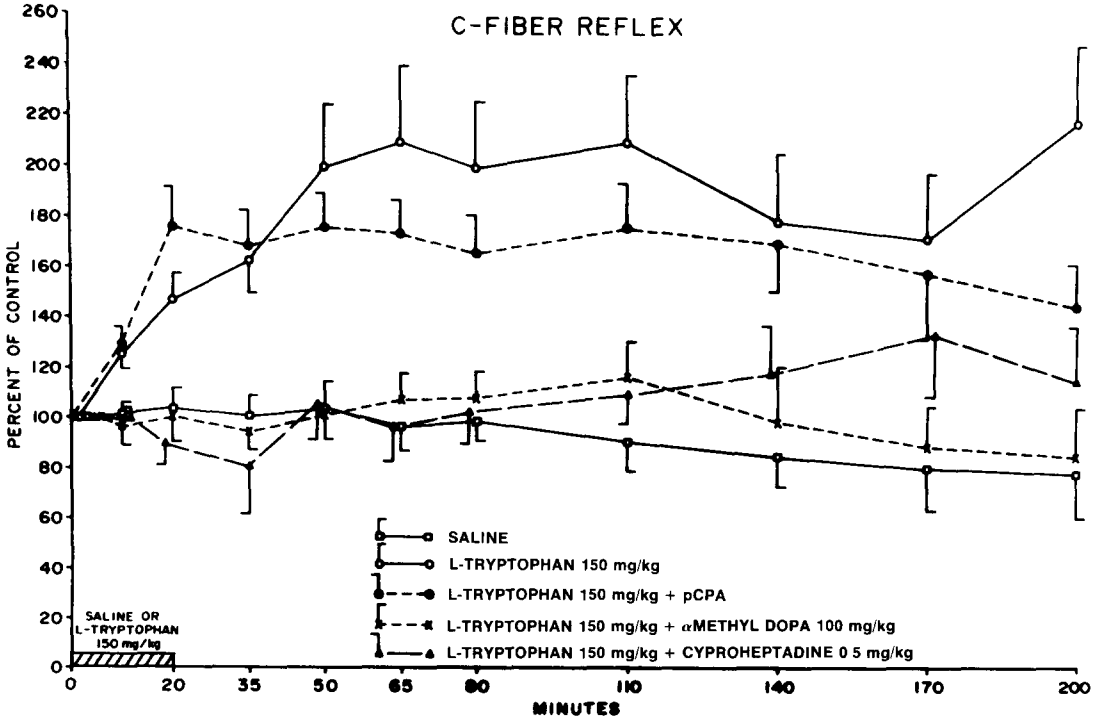

FIG 1 The effect of L-tryptophan 150 mg/kg on the C-fiber reflex L-tryptophan was studied in 17 cats Twelve cats were pretreated with pCPA, 300 mg/kg two doses 48 and 24 hours before L-tryptophan infusion Six cats were treated with α-methyl dopa and five cats were treated with cyproheptadine 1/2 hour before L-tryptophan infusion Eleven cats were used for the saline control The vertical bars represent the standard error of the mean

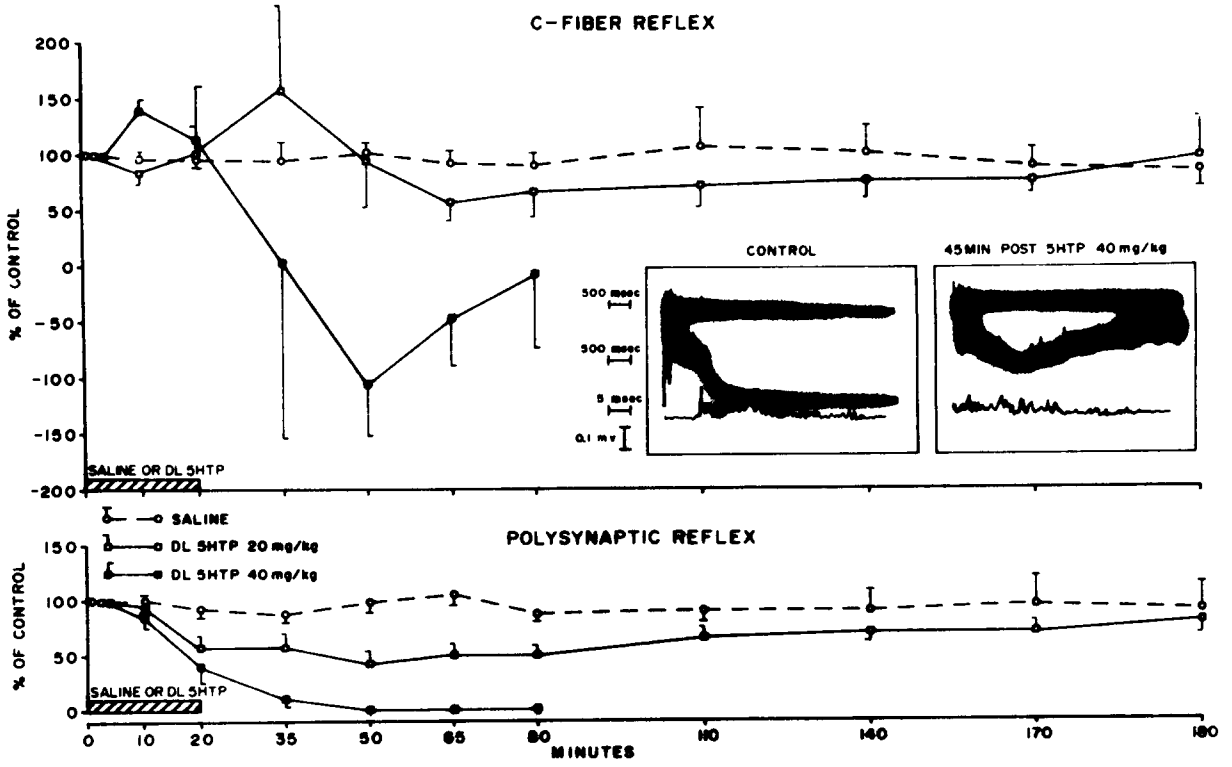

FIG 2 The effect of DL-5-HTP 20 mg/kg on the C-fiber reflex The graph includes data from seven cats injected with saline, five cats administered DL-5-HTP, 20 mg/kg and four cats administered DL-5-HTP, 40 mg/kg The inset shows oscilloscope tracings of potentials recorded from the ventral root The top trace shows action potentials after the stimulus The middle tracing is an integral of the top trace (time constant 0 02 msec) The bottom tract is at a faster sweep speed to demonstrate the short latency polysynaptic potential

rat, guinea pig, dog, cat, steer and man [19,29] (Table 4) It was also identified in the brain of the steer by using thin layer chromotography and was shown to be differentiated from a number of other indolamines To further confirm the existence of tryptamine in the brain as well to establish the brain levels, other techniques were employed including the dansyl chloride method of Snodgrass and Horn [30] and the enzymatic isotopic method of Saavedra and Axelrod [28] Table 5 shows the brain level observed in the rat using these three methods are in close agreement [29] These values also agree with those obtained by a number of other investigators Tryptamine was identified in brain perfusates from the cerebral cortex, hypothalamus, caudate and hippocampus using both spectrophotofluorometric and gas chromotographic methods [17] The concentration appearing in the perfusates of the pentobarbital anesthetized dog was 1–3 ng/ml Tryptamine was found to be ubiquitous in the brain, however, there were regional differences [29]

The physiologic effects of tryptamine were also investigated As already indicated, it produced many autonomic and reflex changes in the chronic spinal dog and in man similar to those produced by LSD The effects of LSD and tryptamine were also studied in male cats with chronically indwelling electrodes to record the electrical activity over the visual, auditory, associational and somaesthetic cortex as well as the hippocampus Electro-oculographic activity was also measured Drugs were injected through an indwelling catheter implanted in the superior vena cava and the animals were observed in sound-proof rooms Both LSD and tryptamine increased wakefulness and decreased REM and spindle sleep in a dose related fashion The duration of action of trypamine was shorter than that of LSD [10]

The effect of LSD, mescaline and DMT on the negative wave of transcallosally evoked cortical potentials of the unanesthetized decerebrate dog was studied Doses of these three hallucinogens which were equipotent in facilitating the flexor reflex had different effects, LSD decreased the negative wave, DMT increased it and mescaline had no effect [27]

It is well known that LSD enhances spinal reflex activity For several reasons the spinal cord actions of LSD and tryptamine seemed particularly amenable to analysis and to this end a number of studies were conducted Our first study shows that methoxamine and tryptamine facilitated both the mono- and polysynaptic reflex of the acute spinal cat [31] Tryptamine and LSD also facilitated the C-fiber reflex in the decerebrated acute spinal cat, and all of these facilitatory actions were antagonized by cyproheptadine but not phenoxybenzamine [1] Tryptophan also facilitated the C-fiber reflex in the acute spinal cat (Fig 1) [3] This action was not antagonized by para-chlorophenylalamine but was antagonized by alpha-methyldopa and cyproheptadine These findings indicated that tryptophan's spinal cord facilitatory actions were a consequence of it being converted to tryptamine and not to serotonin On the other hand, DL-5-hydroxytryptophan inhibited both the C-fiber and the polysynaptic reflex (Fig 2) These observations are consistent with other findings that there are spinal cord serotoninergic nociceptive inhibitory and analgesic mechanisms Tryptaminergic mechanisms are facilitatory

In a series of studies in which brain levels of tryptamine

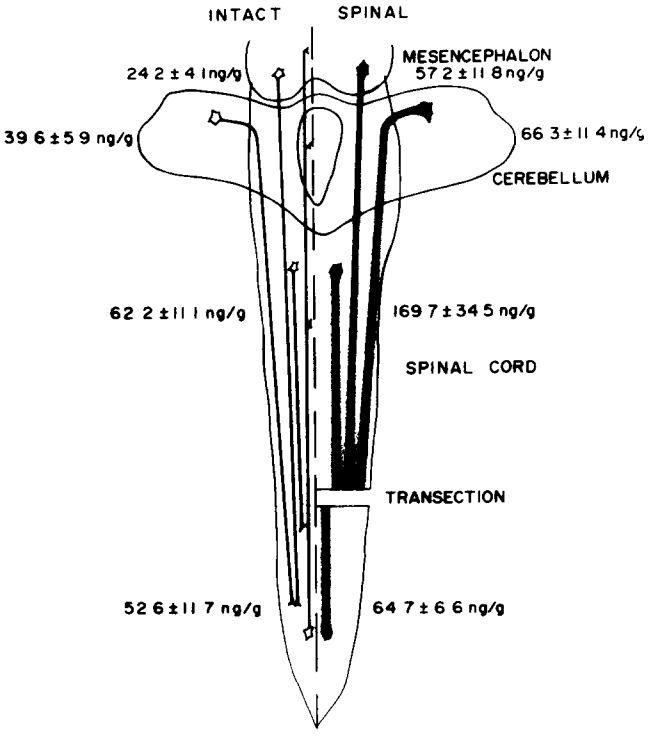

FIG 3 A schematic diagram illustrating hypothetical tryptaminergic pathways in the intact (left side) and the chronic spinal (right side) dog The thickness and coloring of the line illustrate the concentrations of tryptamine (see text)

were compared in the chronic spinal and intact dog, it was found that chronic spinal section increased the levels of tryptamine in the spinal cord above the level of the transection, in the cerebellum and in the mesencephalon (Fig. 3) It, however, either did not alter or slightly elevated the levels in the spinal cord below the level of transection [18] To explain these observations it was assumed that there were both ascending and descending tryptaminergic pathways in the spinal cord, and that when the spinal cord was transected, this resulted in the degeneration of the distal portion of the transected fibers and the accumulation of tryptamine in the proximal portions of both the ascending and the descending fibers To partially test this hypothesis l-tryptophan was shown to markedly enhance the flexor reflex in the acute spinal dog [20] and the C-fiber reflex in the acute spinal cat [2], but did not increase these reflexes in either the chronic spinal dog or cat On the other hand, as previously described, tryptamine and LSD clearly facilitated these reflexes in the chronic spinal dog Further, the facilitatory effect of tryptamine and LSD were greater in the chronic than in the acute spinal dog, suggesting that denervation super-sensitivity had occurred at tryptaminergic receptors Similar observations were made by Nozaki *et al* [26] in the acute and chronic spinal rat who first concluded that denervation supersensitivity had occurred

CONCLUSIONS

Several lines of evidence indicate that tryptamine and LSD-like hallucinogens affect the central nervous system in a similar manner (1) The pattern of autonomic and motor-

TABLE 6

HYPOTHESIS RELATING TO TRYPTAMINE (T), SEROTONIN (5HT) AND NOREPINEPHRINE (NE) AS COTRANSMITTERS AND TO SYNAPTIC SPECIFICITY

Hypothesis	Pre-Synaptic Transmitter(s)	Post-Synaptic Receptor(s)
1	5HT + T	5HT + T (Facilitation)
2	5HT + T	5HT (Inhibition)
	5HT + T	T (Facilitation)
3	NE + T	NE + T (Facilitation)

reflex changes produced by tryptamine in the chronic spinal dog are similar to those produced by LSD-like hallucinogens (2) Dogs tolerant to LSD are cross-tolerant to tryptamine (3) Cyproheptadine and chloropromazine antagonize the effects of tryptamine whereas phenoxybenzamine did not (4) Both tryptamine and LSD produce arousal and decrease REM sleep

Tryptamine is found in all major regions of the brain and has been identified in regional brain perfusates A physiologic role of tryptamine in brain function has been only partially elucidated Several lines of evidence, including the comparison of spinal cord levels of tryptamine in the intact and chronic spinal dogs suggest that there are both ascending and descending tryptaminergic fibers in the spinal cord l-Tryptophan enhances the amplitude of the C-fiber reflex in the acute spinal cat This effect is not antagonized by pCPA which is known to inhibit the hydroxylation of tryptophan to 5-hydroxytryptophan, the immediate precursor of serotonin It is, however, antagonized by the dopa decarboxylase inhibitor, α-methyldopa which inhibits the conversion of l-tryptophan to tryptamine Further, 5-hydroxytryptophan does not enhance, but depresses, the amplitude of the C-fiber and polysynaptic reflexes of the acute spinal cat These findings would strongly argue that tryptophan is producing facilitatory actions on the spinal cord by being converted to tryptamine The site of conversion of tryptophan to tryptamine can be inferred to be in descending pathways, since tryptophan has no facilitatory action in the chronic spinal dog or cat in which descending pathways are presumed to have degenerated, whereas it facilitated spinal cord reflexes in the acute spinal dog and cat It is known that the effects of both tryptamine and LSD are exaggerated in the chronic spinal preparation We feel that these data are consistent with the hypothesis that tryptamine is a neurotransmitter or neurohumor, and that LSD is capable of exerting many of its actions through tryptaminergic receptors

Marsden and Curzon [11] presented evidence that tryptamine is probably synthesized by neurones which contain aromatic amino acid decarboxylases—specifically serotonin, dopamine and presumably other catecholamine containing neurones Thus tryptamine could be functioning as a co-transmitter for these neurones Three alternative hypotheses which are related to the hypothesis that tryptamine is a co-transmitter of 5-HT and NE in neurones modulating the C-fiber reflex are presented in Table 6 Hypothesis 1 which postulates that a 5HT-T neurone synapses with a post-synaptic neurone which has both tryptaminergic and serotoninergic receptors, has been rejected by the experi-

ments referred to However, hypothesis 2 which postulates that a 5-HT-T neurone synapses with two types of neurones, (a) one which has only 5HT receptors and (b) another which has only T receptors, cannot be rejected This hypothesis can be tested only when specific 5HT and T agonists and antagonists can be identified Hypothesis 3 is consistent with not only the evidence reviewed in this paper but with findings showing that there are also spinal cord noradrenergic facilitatory processes Dhawan and Sharma [5] showed that NE applied intrathecally to the spinal cord of the anesthetized cat facilitated mono- and polysynaptic reflexes an effect which was antagonized by dibenamine Methoxamine enhanced the amplitude of the mono- and polysynaptic segmental reflex of the acute spinal cat and these effects can be antagonized by phenoxybenzamine [31] NE injected into the spinal cord of the cat enhanced the mono- and polysynaptic potentials [4] and the C-fiber reflex [22] Methoxamine enhances the flexor reflex and evokes the stepping reflex of the chronic spinal dog and these effects are antagonized by phenoxybenzamine Experiments conducted to clarify the mechanisms whereby noradrenergic processes facilitated nociceptive reflexes, showed that there were two facilitatory processes, one involving spinal cord descending noradrenergic pathways, and the other involving ganglionic sympathetic noradrenergic neurons and fibers which enter the spinal cord with blood vessels principally by way of the anterior median fissure [23, 24, 25, 26] As a consequence of this dual facilitatory action, stimulation of these two noradrenergic pathways enhanced the flexor reflex in both the acute and chronic spinal rat acting primarily on the descending pathway in the acute spinal rat and on the sympathetic-spinal pathway in the chronic spinal rat in which denervation sensitization had occurred Hence, it was not possible to unambiguously assess the role of descending noradrenergic pathways in facilitating the flexor reflex by cord transection experiments Further, although hypothesis 3 is consistent with existing data, critical experiments have not been done to determine if the descending tryptaminergic pathway is the same as the descending noradrenergic pathway

It is possible however that there are other synaptic systems including ones involving epinephrine, dopamine, other indole-, catechol- and phenethylamines and even histamine in which tryptamine could also serve as a cotransmitter, and in which other post-synaptic receptors of different specificities may be involved It will be an important pharmacologic and physiologic challenge to determine the calculus of cotransmitters at neurons and receptors—that is, how their diverse influences at the synapse influence postsynaptic neuronal excitability and firing It is not hard to imagine how minor pertubations of a cotransmitter could cause pathologic functioning of neuronal systems and networks As we proceed in our pharmacologic analysis of synaptic events it is important to recognize that there is not only receptor specificity but also synaptic specificity within brain functional systems, and that these two types of specificities are important in both the physiology of neuronal networks, but also in the action of drugs To illustrate the principle of synaptic specificity, a synapse may involve 2 transmitters and only one post-synaptic receptor type, 2 transmitters and 2 receptor types or 1 transmitter and 2 receptor types If these types of concatenations exist, they may explain some of the disparate permutations that are seen when attempts are made to reconcile physiologic and pharmacologic observation

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