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The Nature of Opioid and LSD Receptors: Structural Activity Relationship Implications

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The structural activity relationships of the drugs under consideration are inexorably entwined with receptors and receptor theory since they have been clearly demonstrated to have agonistic and antagonistic activity. It also appears that their pharmacologic effects are in some way related to neurotransmitters and neuromodulators. The discovery of the endorphins and enkephalins and the similarities of some of their effects to those of the narcotic analgesics has given rise to a most exciting chapter of pharmacology. Over a period of nearly three decades, a pharmacology of the LSD-like hallucinogens has been emerging which suggests that they too may intereact with several receptors. In this presentation, I wish to discuss some concepts that are emerging concerning receptor topology and drug selectivity which bear directly on receptor classification and which have relevance to SAR of these two groups of drugs.

NARCOTIC ANALGESICS

A number of investigators have studied the SAR of narcotic analgesics. For the most part, the data on which these studies have been based have been generated in several species using different measures of pharmacologic effects such as analgesia. Table 1 presents data on seven critical drugs that have great theoretical significance in discussing their structural activity relationships. Morphine is used as a standard drug against which the others are compared. However, it should be recognized that morphine may have several modes of action and interact with more than one receptor (Martin et al. 1976; Gilbert and Martin 1976).

Normorphine is a weak analgesic in the mouse, is 1/6 to 1/3 as potent as morphine in man and in binding assays, equipotent to morphine on the guinea pig ileum but devoid of morphine like activity in the dog.

Metazocine is an agonist approximately equipotent to morphine in the mouse, dog and man. It is clearly a strong agonist in the dog, but has been characterized as an agonist-antagonist by Pert and Snyder (1974) on the basis of data from binding studies having a relatively low NaCl/no NaCl ratio (6).

Phenazocine is some 10 times more potent than morphine on measures

presented in Table 1, yet was only 1/5 as potent as morphine in suppressing abstinence in the monkey.

N-allyl normetazocine (SKF 10047) is virtually devoid of analgesic activity but produces delirium and hallucinations in man and delirium in the dog. These effects can be antagonized by naloxone.

Meperidine is an effective analgesic in man and the mouse; is much less potent relative to morphine on the guinea pig ileum and in binding studies. In man it will partially suppress abstinence in morphine dependent subjects (Himmelsbach 1942). Further, it has a limited ability to produce physical dependence in man (Himmelsbach 1942, 1943). Of particular interest is the observation that nalorphine was nearly ineffective in precipitating abstinence in meperidine dependent patients (Isbell 1955). In the dog, meperidine is devoid of morphine-like activity (Gilbert and Martin 1976) and will not produce physical dependence (Carter and Wikler 1955). Although it is relatively impotent in inhibiting the electrically stimulated guinea pig ileum and in preventing binding of naloxone to rat brain homogenate, it is qualitatively similar to morphine in these preparations.

These data have been analyzed by calculating correlation coefficients between the various measures and this analysis is presented in Table 2. As can be seen, the only significant regression was between the mouse and dog. Many of the correlation coefficients were highly significant which stresses the weakness of this technique for analysis of this type of data.

LSD-LIKE HALLUCINOGENS

There are both theoretical and practical problems of defining the group of drugs considered LSD-like hallucinogens. The discussion of these drugs will be restricted largely to data generated in the spinal dog, man and rat. An LSD-like hallucinogen should, of course, have pharmacologic activity like LSD. The effects of LSD can be divided into several categories including: (1) Somatomotor and autonomic; facilitation of the patellar (man) and flexor reflex (spinal dog), evocation of the stepping reflex (spinal dog), tachycardia (dog and man); increased blood pressure (man); mydriasis (man and dog), tachypnea (man and dog) and increased body temperature (man and dog). (2) Subjective and behavioral changes; euphoria, delusion and hallucinations (man); arousal, restlessness, tracking and starting (dog) and the alteration of operant behavior (rat). (3) The development of tolerance and the conferring of cross tolerance. (4) The blocking of the effects with more or less specific antagonists. Thus chlorpromazine and cyproheptadine will antagonize this effect of LSD-like hallucinogens but not phenoxybenzamine.

As can be imagined the permutations of these attributes are large and from a practical point of view resources allow only the study of certain ones. Because of differences in biases of investigators, certain aspects of the action of certain putative LSD-like hallucinogens are focused on. For this reason, very little quantitative comparable data has been generated which allows hard

TABLE 1

POTENCY OF SEVERAL OPIOID AGONISTS AND ANTAGONISTS ON DIFFERENT TEST SYSTEMS

	MOUSE HOT PLATE[a]	DOG[b,c]	MAN[d]	GUINEA PIG ILEUM[e]	RAT BRAIN[f,g] BINDING NO NaCl	SITES 100 Mn NaCl
MORPHINE	1	1	1	1	1(3)	1(110)
NORMORPHINE	.05	0	.35	1	.2(15)	.16(700)
METAZOCINE	.9	1.3	.8	.4	.3(10)	1.8(60)
PHENAZOCINE	13	8.3	3	10	5(.6)	14(8)
PENTAZOCINE	0.1	.3	.17	.45	.2(15)	2.2(50)
N-ALLYL NOR-METAZOCINE	0	0	0	1	1.5(2)	37(3)
MEPERIDINE	.21	0	.13	.06	.001(3000)	.002(50,000)

POTENCIES ARE EXPRESSED AND THE NUMBER MGS OF MORPHINE EQUIVALENT TO 1 MG OF THE DRUG. THE FIGURES IN PARENTHESIS ARE THE CONCENTRATIONS IN nM THAT PRODUCE 50% INHIBITION OF BINDING. THE VALUES 0 INDICATE THAT THE DRUG HAS NO ACTIVITY ON THE GIVEN MEASURE.

a. Pert et al. 1976; b. Martin et al. 1976; c. Gilbert and Martin 1976;
d. data from the work of Houde; e. Kosterlitz and Waterfield 1975;
f. Pert and Snyder 1973; g. Pert and Snyder 1974.

TABLE 2

PRODUCT MOMENT CORRELATION COEFFICIENTS (r), SLOPES (b) WITH STANDARD ERROR OF ESTIMATE ($s_{y.x}$) FOR DATA PRESENTED IN TABLE 1

		Mouse Analgesia Hot Plate	Dog Depression of the Flexor Reflex	Man Analgesia	Guinea Pig Ileum	Rat Brain Binding No NaCl
DOG	r	$.99^{.01}$				
	b	$.63^{.05}$				
	$s_{y.x}$	.27				
MAN	r	$.96^{.01}$	$.98^{.01}$			
	b	.21	1.17			
	$s_{y.x}$	.26	.59			
GUINEA PIG	r	$.99^{.01}$	$.98^{.01}$	$.94^{.01}$		
	b	.75	1.15	3.14		
	$s_{y.x}$	.44	.67	.73		
BINDING (RAT) NO NaCl	r	$.95^{.01}$	$.94^{.01}$	$.90^{.01}$	$.97^{.01}$	
	b	.35	.55	1.52	.48	
	$s_{y.x}$	.50	.56	.73	.39	
BINDING (RAT) 100 NM NaCl	r	.16	.13	.01	.23	.42
	b	.45	.60	.17	.90	3.28
	$s_{y.x}$	12.51	12.55	12.67	12.31	11.47

SUPERSCRIPT INDICATES LEVEL OF SIGNIFICANCE

comparisons which are useful for SAR considerations. At the present time, it seems that LSD-like hallucinogens may act through at least two mechanisms of action; a tryptaminergic and serotonergic mechanism (Martin and Sloan 1977). The relative importance of these two mechanisms in mediating different signs and systems has not been ascertained at this time.

Table 3 and table 4 present comparisons of the effects of several important drugs that are related in one way or another to LSD. LSD is the prototypic drug against which the others are compared.

Psilocin and its phosphorylated congener, psilcybin,appear to be very similar to LSD in their pharmacology. However, there is a marked difference between the potency of psilocin in man and its ability to prevent the saturable binding of 5HT and LSD in rat brain homogenate on the one hand and in the dog on the other. Further, LSD tolerant rats were not cross tolerant to psilocin. The time course of brain concentration has not been studied (or even plasma level) in these species so differences in distribution, metabolism or excretion cannot be excluded as reasons for differences in potency. Since both LSD and psilocin have a rapid onset and a prolonged duration of action, differences in distribution, metabolism or excretion probably do not explain the differences in potency in different test systems. Differences in affinity between psilocin and LSD for the receptor are another possibility which, if true, could indicate a subtle species difference in receptor topography.

DMT is less potent in man than it is in the dog. Further, cross tolerance to DMT in both LSD tolerant man and chronic spinal dogs is not complete and is seen for certain signs and symptoms but not for others.

A critical drug is BOL. It is questionable whether it can produce LSD-like effects in man. Chronically administered BOL conferred some cross tolerance to LSD in man (Isbell et al. 1959). In doses up to 1 mg/kg intravenously BOL is devoid of LSD-like activity. In the rat, BOL inhibits operant behavior and tolerance develops to this effect with chronic administration (Appel and Freedman 1968). Whether the BOL tolerant rat is cross tolerant to LSD cannot be answered. Some tolerance was seen but it was not statistically significant. The LSD tolerant rat may exhibit some tolerance to BOL but it too was not statistically significant. BOL on the other hand is nearly as potent as LSD in inhibiting the binding of both LSD and 5HT to the brain. BOL is neither an agonist or antagonist in man (Isbell et al. 1959).

DISCUSSION

The first point that these data suggest is that there are small but significant differences in receptors between species. To illustrate this point for both the opioid-like analgesics and LSD-like hallucinogens the following contrasts are reviewed:

(1) Normorphine appears to resemble morphine in the mouse and guinea pig ileum but is devoid of morphine activity in the dog.

TABLE 3

POTENCY OF SEVERAL LSD-LIKE HALLUCINOGENS IN MAN, DOG AND RAT AS WELL AS THEIR ABILITY TO INDUCE TOLERANCE AND CROSS TOLERANCE

	MAN	DOG[a]	RAT[b]	RAT BRAIN BINDING[c] 5HT	RAT BRAIN BINDING[c] LSD
LSD	1 (T)	1 (T)	(T)	1	1
PSILOCIN	.014 (T;CT)	1 (CT)		.01	.008
PSILOCYBIN			T (CT)		
MESCALINE	.0003 (T;CT)	.004 (CT)	T (CT)		
DMT	.003 (Partial T)	.1 (Partial T)		.05	.004
2-BROMO-LSD (BOL)	0 (CT)	0	T (no Sig. CT)	.1	.8

T in parenthesis indicates that chronic administration of the drug induced tolerance. CT indicates that the LSD tolerant animal was cross tolerant to the drug. The papers of Isbell which were summarized by Martin and Sloan (1977) and Martin et al. (1978) are the primary source of the data in man. (a) Martin et al. (1978); (b) Appel and Freedman (1968); (c) Bennett and Snyder (1976). 0 indicates that the drug was without effect.

TABLE 4

PRODUCT MOMENT CORRELATION COEFFICIENTS (r), SLOPES (b) WITH STANDARD ERROR OF ESTIMATE ($s_{y.x}$) FOR DATA PRESENTED IN TABLE 3

		MAN	DOG	RAT
DOG	r	.62		
	b	.74		
	$s_{y.x}$	.37		
RAT 5HT	r	$1.00^{.01}$	.52	
	b	.95	.44	
	$s_{y.x}$	.04	.35	
RAT LSD	r	.69	.07	0.74
	b	.72	.06	0.82
	$s_{y.x}$	.33	.45	0.30

SUPERSCRIPT INDICATES LEVEL OF SIGNIFICANCE

(2) Metazocine is a typical morphine-like drug in man, dog, mouse and guinea pig ileum but appears to resemble other agonists-antagonists in rat brain binding studies.

(3) Phenazocine is a very potent morphine-like agonist in man and dog, but a much weaker and less effective agonist in the monkey.

(4) N-allylnormetazocine (SKF 10047) is devoid of morphine-like activity in the mouse, dog and man, but is equipotent to morphine on the guinea pig ileum.

(5) BOL produces effects similar to LSD in the rat but is nearly if not totally devoid of LSD-like activity in the man and the dog.

The most probable explanation of these differences is that the receptors differ in their intimate details from one preparation to another. The critical dimension could be species or tissue (e.g. brain vs. gut) or even different brain regions or different functional systems. It may thus be important in SAR studies to treat species or even varieties as an independent variable.

Perhaps the next level of receptor classification should be subspecies. Recently there has been increasing evidence that there are subspecies of opioid receptors (Martin 1967; Martin et al. 1976; Lord et al. 1977). I suspect that it will be demonstrated that there are subspecies of the serotonin and tryptamine receptors also and that these subspecies may also be in different functional systems. Thus with regard to the opioid receptors, μ agonists produce one type of analgesia as measured by the tail flick or hot plate while κ agonists produce another which can be measured using the writhing test or the flexor reflex. It is important for SAR consideration that the data be homogeneous and indicative of one pharmacologic action. This is important because many agonists and antagonists are mixed, having several modes of actions.

Another important attribute of agonists is their intrinsic activity. Partial agonists of the μ type (profadol, propiram and buprenorphine) and κ type (nalorphine) have been identified. An important attribute of partial agonists as they relate to SAR considerations is that potency determinations will underestimate affinity.

As we attempt to understand the relationship of the chemical structure of drugs, the nature of receptors and pharmacologic actions, our theories have become more sophisticated which in turn necessitates more precise and well designed experiments.

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