Lehmann, A. (1967). Audiogenic seizure data in mice supporting new theories of biogenic amines mechanisms in the central nervous system. Life Sci. 6, 1423-1431.

Wada, J.A., Balzamo, E., Meldrum, B.S. and Naquet, R. (1972). Behavioral and electrographic effects of L-5-hydroxytryptophan and DL-parachlorophenylalanine on epileptic Senegalese baboon (Papio papio). EEG Clin. Neurophysiol. 33, 520-526.

COMPARISON OF THE EFFECTS OF R-(-)-2-AMINO-1-(2,5-DIMETHOXY-4-METHYL-PHENYL) PROPANE (DOM), R-(-)-2-AMINO-1-(2,5-DIMETHOXY-4-METHYLPHENYL) BUTANE (BL-3912A) AND 5-HYDROXYTRYPTAMINE ON NON-INNERVATED VASCULAR SMOOTH MUSCLE.

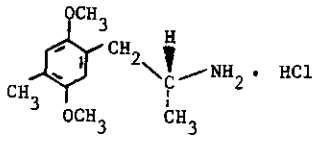
Donald C. Dyer
Department of Anatomy, Pharmacology, Physiology, College of Veterinary Medicine, Iowa State University, Ames, Iowa 50011

ABSTRACT

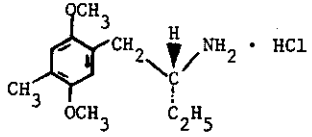
Isolated strips of sheep umbilical arteries contracted in the presence of R-(-)-2-amino-1-(2,5-dimethoxy-4-methylphenyl) butane (BL3912A). These contractions faded over an hour period and at this time BL3912A antagonized contractions to R-(-)-DOM, 5-hydroxytryptamine (5-HT) but not to angiotensin. The initial contraction produced by BL3912A was antagonized by cinanserin, a 5-HT antagonist. These experiments indicate that BL3912A can be classified as a partial agonist of 5-HT receptors in sheep umbilical arteries.

INTRODUCTION

A variety of substituted phenylisopropylamines possess psychotomimetic activity (Snyder et al., 1968, Shulgin et al., 1969). DOM is an example of such a drug. Hallucinogens of this type appear to produce their central effects (Horita and Hill, 1972) and stimulation of umbilical vasculature via activation of a 5-hydroxytryptamine (5-HT) receptor system (Dyer, et al., 1973). BL3912A (2-amino-1-(2, 5-dimethoxy-4-methylphenyl) butane is closely related chemically to DOM (figure 1) yet only preliminary studies have been reported regarding its central nervous system activity (Coppola, 1974). BL3912A increased blood pressure in conscious dogs but decreased blood pressure in anesthetized dogs (Buyniski, et al., 1974). The receptors mediating these effects are unknown. The purpose of this study was to ascertain the effects of BL3912A on the umbilical vasculature and to classify the receptors upon which it acts.



R-(-)-2-amino-1-(2,5-dimethoxy-4-methylphenyl) propane hydrochloride (DOM)



R-(-)-2-amino-1-(2,5-dimethoxy-4-methylphenyl) butane hydrochloride (BL-3912A)

Figure 1 - Structure of DOM and BL-3912A.

TABLE 1

Effect of Cinanserin on Responses to BL3912A

	Percent Response (5-HT = 100%)		
	N	Control (±SEM)	Cinanserin (±SEM)
BL3912A(10^{-6}M)	4	16.5 (±3.9)	0.0
BL3912A(10^{-5}M)	4	30.5 (±6.7)	1.2 (±1)
BL3912A(10^{-4}M)	4	38.0 (±5.5)	30.3 (±6.5)

Paired tissues were maximally contracted with 5-HT. Following wash out and relaxation, one tissue in each pair was pretreated with cinanserin (3×10^{-7} M, 30 min). At the end of the incubation period each bath in the pair received a single administration of BL3912A.

METHODS

Sheep umbilical cords were obtained as previously described (Dyer, 1970). Strips of umbilical artery approximately 2 cm long were suspended in Krebs solution in 10 ml isolated organ baths. The baths were maintained at 37°C and oxygenated by bubbling a mixture of oxygen-carbon dioxide (95:5) through the bottom of the bath. The contractions were magnified X10 and recorded isotonically on a kymograph drum.

BL3912A produced dose dependent contractions of sheep umbilical arteries. These contractions were antagonized by prior treatment with cinanserin (Table 1). When BL3912A was left in the bath for one hour the contraction faded towards the control baseline. If at this time

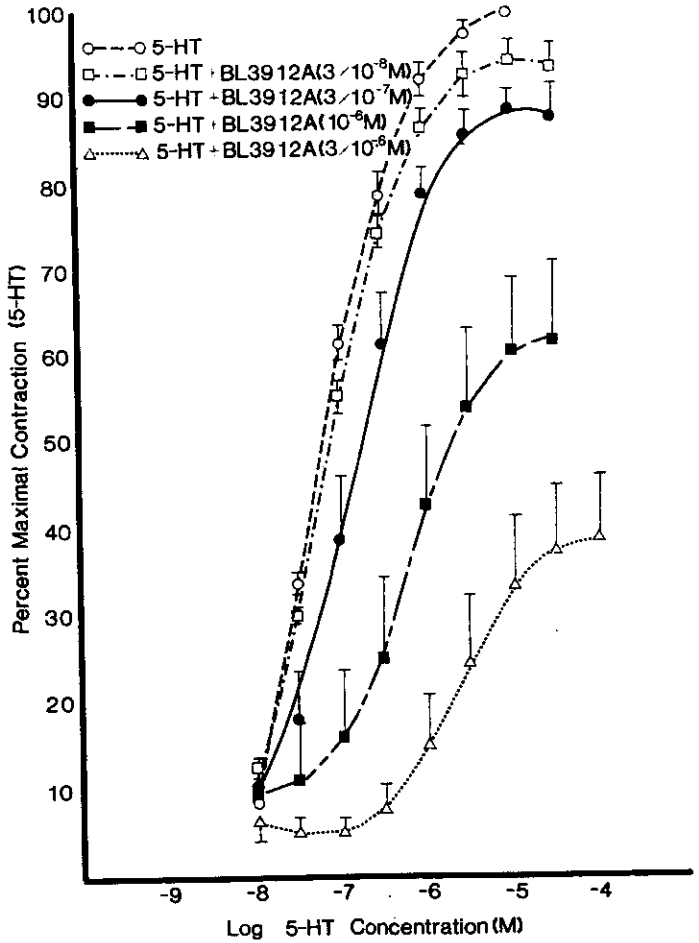


Figure 2 Dose-response relationships of 5-HT on umbilical arteries exposed to specific concentrations of BL3912A for one hour. Vertical bars are ± S.E.M. of 5 to 7 experiments.

5-HT was added to the bath in a cummulative manner, antagonism to 5-HT was observed (Figure 2). In a similar manner BL3912A also antagonized responses to DOM (Figure 3). To rule out the possibility that this antagonism was due to non-specific smooth muscle depression, angio-

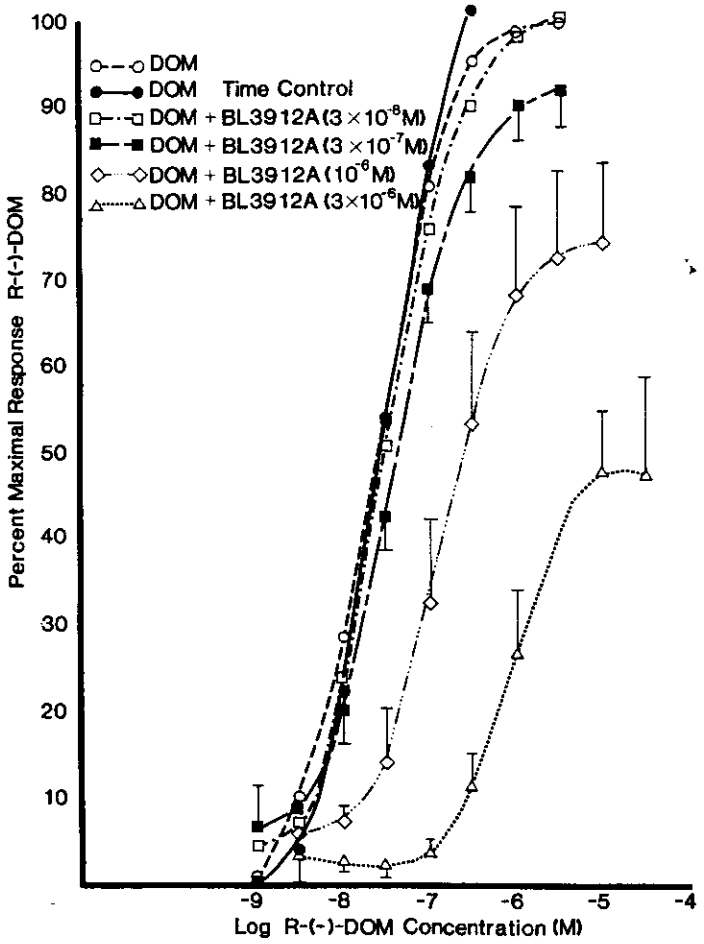


Figure 3 Dose-response relationship of R-(-)-DOM on umbilical arteries exposed to specific concentrations of BL3912A for one hour. Vertical bars are ± S.E.M. of 5 experiments.

tensin was used as an agonist. Angiotensin is a potent agonist on sheep umbilical arteries and appears to act in a direct manner. Concentrations of BL3912A ($> 10^{-6}$M) which greatly antagonized contractions to 5-HT and DOM failed to alter responses to angiotensin (Figure 4).

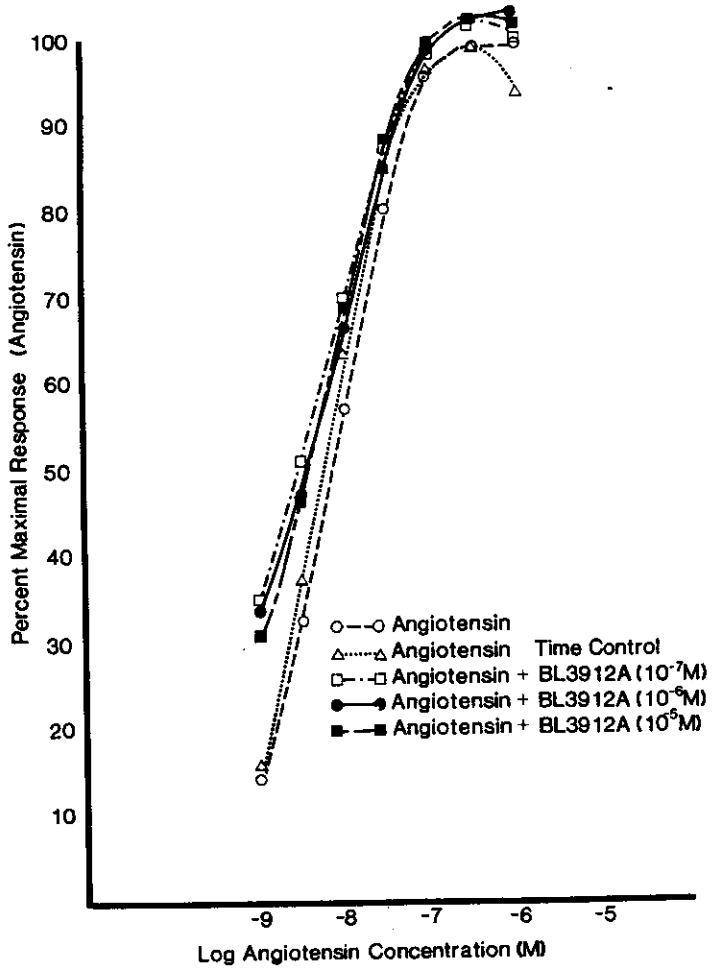


Figure 4 Dose-response relationship of angiotensin on umbilical arteries exposed to specific concentrations of BL3912A for one hour. Points on the curves are the means of 4 experiments. Standard error bars are omitted for the sake of clarity.

DISCUSSION

The evidence from these experiments suggests that BL3912A is able to activate 5-HT receptors as does DOM (Dyer et al., 1973). However,

DOM is significantly more potent. BL3912A is also able to antagonize responses to 5-HT and DOM. This antagonism appears to be rather specific in that it does not extend to angiotensin. This study indicates that BL3912A can be classified as a partial 5-HT agonist.

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REFERENCES

Buyniski, J.P., Smith, M.L. and Bierwagen, M.E. (1974). Cardiovascular and gross behavioral effects of amphetamine, 2-amino-1-(2,5-dimethoxy-4-methylphenyl) propane (DOM) and 2-amino-1-(2,5-dimethoxy-4-methylphenyl) butane (BL3912A) in the conscious dog. Res. Comm. Chem. Path. Pharmacol. 8, 213-221.

Coppola, R. J. (1974). An evaluation of 1-(4-methyl-2,5-dimethoxyphenyl-2-aminobutane (MDPA-1) as an enhancer of memory and learning. J.A.O.A. 73, 406-411.

Dyer, D. C. (1970). The pharmacology of isolated sheep umbilical cord blood vessels. J. Pharmacol. Exp. Ther. 175, 565-570.

Dyer, D. C., Nichols, D. E., Rusterholz, D. B. and Barfknecht, C. F. (1973). Comparative effects of stereoisomers of psychotomimetic phenylisopropylamines. Life Sci. 13, 885-896.

Horita, A. and Hill, H. F. (1972). Hallucinogens, amphetamines and temperature regulation. In "The pharmacology of thermoregulation", symposium, San Francisco, Karger, Basel, 417-431.

Shulgin, A. T., Sargent, R. and Naranjo, C. (1969). Structure activity relationships of one ring psychotomimetics. Nature 221, 537-541.

Snyder, S. H., Faillace, L. A. and Weingartner, H. (1968). DOM (STP), a new hallucinogenic drug, and DOET: Effects in normal subjects. Amer. J. Psychiat. 125, 113-120.

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PROSTAGLANDIN BIOSYNTHESIS AND METABOLISM IN RAT BRAIN SLICES*

Crystal A. Leslie**

Department of Biochemistry
Brandeis University, Waltham, Massachusetts 02154

Abstract

Prostaglandin $F_{2\alpha}$ and E were measured in the slices and in the media after incubation of rat brain slices. About 5 to 10 times more prostaglandin $F_{2\alpha}$ than prostaglandin E was found, most of which was secreted into the media. In the absence of oxygen or in the presence of indomethacin, prostaglandin levels in both the slices and media were reduced. Serotonin, norepinephrine, epinephrine, and DOPA, at 10^{-3} M concentrations, increased the prostaglandin $F_{2\alpha}$/E ratio in both the media and slices. The levels of prostaglandins $F_{2\alpha}$ found in the slices and media when the slices were incubated with prostaglandin E_2 increased significantly, this increase being independent of the presence of indomethacin. This suggests that prostaglandin E_2 was being converted to $F_{2\alpha}$ by a prostaglandin E_2 9-ketoreductase in the rat brain slices.

Introduction

An understanding of the biosynthesis and catabolism of the prostaglandins, participating as they do in so many physiological processes and responses, must be of enormous value in the elucidation of normal and pathological body states.

Among the list of tissues containing prostaglandins is nervous tissue. Prostaglandin (PG) synthetase activity has been demonstrated in microsomal fractions of brain homogenates after addition of an external source of PG precursors (1). Prostaglandins have been reported to be released into the circulation when sympathetic nerves are stimulated (2) and PGE inhibits the release of norepinephrine from nerve fibres (3). Biogenic amines are known to stimulate synthesis of prostaglandins in homogenized tissues other than brain. Serotonin, norepinephrine, and epinephrine stimulate synthesis of PGE_2 in bovine seminal vesicle microsomal fractions (4), and PG synthetase activity of rat stomach fundus was significantly stimulated by L-norepinephrine, L-epinephrine, and dopamine (5). Since many of the biogenic amines are located in the central

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