J. Pharm. Pharmacol. 1984, 36: 213–214
Communicated September 14, 1983

Ha-117 and Ha-118 are potent dopamine receptor agonists*

MUSTAFA ILHAN, JOHN P. LONG**, JOSEPH G. CANNON, *Departments of Pharmacology** and Medicinal Chemistry, College of Medicine and Pharmacy, University of Iowa, Iowa City, Iowa, 52242, USA.*

In-vitro studies evaluated the presynaptic dopamine receptor activities of *trans*-*N*-propyl-7,9-dihydroxyoctahydrobenzo[f]quinoline (Ha-117) and *trans*-*N*-ethyl-7,9-dihydroxyoctahydrobenzo[f]quinoline (Ha-118) using isolated field-stimulated cat right atria. Ha-117 and Ha-118 were found to be potent dopamine receptor agonists since their effects were antagonized by haloperidol. Compounds were inactive on presynaptic α_2-adrenoceptors using rat vas deferens and guinea-pig ileum. Results show that both resorcinol derivatives of octahydrobenzo[f]quinoline are potent dopamine receptor agonists without having presynaptic α_2-adrenoceptor stimulating activity.

Dopamine receptor agonists have been reported to reduce the tachycardia elicited by transmural electrical stimulation of cat right atria through stimulation of presynaptic dopamine receptors (Ilhan et al 1976). In this study we attempted to evaluate the dopaminergic properties of two new heterocyclic congeners of dopamine, *trans*-N-propyl-7,9-dihydroxyoctahydrobenzo-[f]-quinoline (Ha-117) and *trans*-N-ethyl-7,9-dihydroxyoctahydrobenzo[f]quinoline (Ha-118). Since most of the potent dopaminergic agonists have presynaptic α_2-adrenoceptor stimulating activity (Maixner et al 1983) we evaluated the compounds using coaxially stimulated guinea-pig ileum and transmurally stimulated rat vas deferens for their possible presynaptic α_2-adrenoceptor stimulating properties.

Cats were anaesthetized by i.p. injection of sodium pentobarbitone (30 mg kg^{-1}). Following midline thoracotomy the heart was excised. Right atrium was isolated and suspended between 2 platinum electrodes in a 100 ml organ bath containing Feigen solution (mM): NaCl 154·0; KCL 5·6; $NaHCO_3$ 23·8; $CaCl_2$ 5·6 and glucose 11·1. Atrium was transmurally stimulated at 2 Hz, 5 ms duration and 100 V for 10 s. Atrial rate was monitored with a Beckman Model 9857B cardiotachometer.

Isolated guinea-pig ileum was stimulated coaxially with 0·1 Hz, 1 ms duration and 100 V in Tyrode solution (mM): NaCl 137·9; KCl 2·7; $CaCl_2$ 1·8; $MgCl_2$ 1·1; NaH_2PO_4 0·4; $NaHCO_3$ 11·9 and glucose 11·4. Isolated rat vas deferens was transmurally stimulated with 10 Hz, 3 ms duration and 120 V, 0·1 TPS (train rate) and 100 ms train duration in Krebs solution (mM): NaCl 113·8; KCl 4·7; $CaCl_2$ 2·4; KH_2PO_4 1·2; $MgSO_4$ 1·2; $NaHCO_3$ 25·0 glucose 11·4.

All solutions were aerated with 95% O_2 and 5% CO_2 and were maintained at 37 °C. A Statham force displacement transducer, Beckman recorder and Grass S48 stimulator were used. Ten ml organ bath was used for guinea-pig ileum and rat vas deferens experiments.

Data are expressed as mean ± s.e.m. IC50 values and 95% confidence intervals were determined by probit analysis. A 2 × 2 parallel line bio-assay procedure as described by Finney (1952) was used in the determination of parallelism.

Table 1 shows that both Ha-117 and Ha-118 produce inhibition of the stimulation-induced heart rate increase which was antagonized by dopaminergic antagonist haloperidol. The concentration-response curves of compounds alone and in the presence of haloperidol (1.3×10^{-7} M) were parallel. Isoproterenol ($4{\cdot}0 \times 10^{-9}$ M)-induced tachycardia (46·0 ± 5·9 beats min^{-1}) (n = 5) was not altered by Ha-117 or Ha-118. Tachycardic responses to isoproterenol were 46·8 ± 6·1 (n = 5) and 45·8 ± 5·7 beats min^{-1} (n = 5) in the presence of Ha-117 ($2{\cdot}9 \times 10^{-8}$ M) or Ha-118 ($3{\cdot}0 \times 10^{-8}$ M) respectively.

Highest concentrations of Ha-117 ($2{\cdot}9 \times 10^{-5}$ M) and Ha-118 ($3{\cdot}0 \times 10^{-5}$ M) were found inactive in stimulation-induced twitch responses of guinea-pig ileum (n = 5) and rat vas deferens (n = 5), although clonidine ($4{\cdot}3 \times 10^{-8}$ M) abolished the twitch responses

Table 1. The inhibitory effects of Ha-117 and Ha-118 on trasmural stimulation-induced heart rate increase of isolated cat right atria. IC50 of Ha-117 and Ha-118 were $1{\cdot}0 \times 10^{-8}$ M ($8{\cdot}2 \times 10^{-9} - 1{\cdot}3 \times 10^{-8}$ M) and $1{\cdot}4 \times 10^{-8}$ M ($1{\cdot}1 \times 10^{-8}$ M – $2{\cdot}0 \times 10^{-8}$ M) respectively.

Drug	Concentration (M)	Inhibition (as % of controls) Alone	In the presence of haloperidol ($1{\cdot}3 \times 10^{-7}$ M)
Ha-117 (n = 5)	$2{\cdot}9 \times 10^{-9}$	29·6 ± 2·7	0
	$8{\cdot}8 \times 10^{-9}$	51·6 ± 4·2	0
	$2{\cdot}9 \times 10^{-8}$	70·2 ± 4·0	0
	$8{\cdot}8 \times 10^{-7}$	—	12·8 ± 5·7
	$2{\cdot}8 \times 10^{-6}$	—	40·0 ± 8.5
	$8{\cdot}8 \times 10^{-6}$	—	52·0 ± 10·5
Ha-118 (n = 5)	$3{\cdot}0 \times 10^{-9}$	14·4 ± 3·0	0
	$9{\cdot}1 \times 10^{-9}$	44·4 ± 4·6	0
	$3{\cdot}0 \times 10^{-8}$	65·2 ± 4·2	0
	$9{\cdot}1 \times 10^{-7}$	—	24·0 ± 3·2
	$3{\cdot}0 \times 10^{-6}$	—	40·8 ± 2·9
	$9{\cdot}1 \times 10^{-6}$	—	58·6 ± 4·4

* This work was supported in part by Grants from the United States Public Health Service—GM-22365 and HLB-28313.

** Correspondence.

to electrical stimulation in these preparations through the stimulation of presynaptic α_2-adrenoceptors.

The present results provide strong evidence that both resorcinol derivatives of octahydrobenzo[f]quinoline are potent dopamine receptor agonists without having presynaptic α_2-adrenoceptor stimulating activity.

REFERENCES

Finney, D. J. (1952) Statistical Methods in Biological Assay. Charles Griffen & Co., London

Ilhan, M., Long, J. P., Cannon, J. G. (1976) Arch. Int. Pharmacodyn. Ther. 219: 193–204

Maixner, W., Flynn, J. R., Arnerić, S. P., Cannon, J. G., Long, J. P. (1983) J. Pharmacol. Exp. Ther. 224: 352–358

J. Pharm. Pharmacol. 1984, 36: 214–216
Communicated July 29, 1983

Influence of smoking on serum protein composition and the protein binding of drugs

I. H. BENEDEK, R. A. BLOUIN, P. J. MCNAMARA*, *College of Pharmacy, University of Kentucky, Lexington, KY 40536-0053, USA.*

The influence of smoking on α_1-acid glycoprotein (α_1-AGP) and serum albumin concentrations and the protein binding of phenytoin and propranolol in healthy volunteers was investigated. α_1-AGP concentrations were found to be statistically different ($P < 0.05$) in the smokers (mean = 84·3 mg dl^{-1}) versus non-smokers (mean = 62·8 mg dl^{-1}). There was a trend for lower serum albumin concentrations and lower fraction unbound of propranolol in the smokers. Smoking did not affect the protein binding of phenytoin.

Studies involving the role of cigarette smoking on drug disposition have focused primarily on the induction of drug-metabolizing enzymes. However, two reports on the influence of smoking on plasma protein binding have been published. In one study (Rose et al 1978), no difference in phenytoin serum protein binding between smoking and non-smoking groups was found. In the other study (McNamara et al 1980), the extent of lidocaine (lignocaine) binding was greater in serum obtained from smokers than in the serum of non-smokers. Although not specifically measured, it was suggested that the cause of this increase in lidocaine binding might be related to elevated concentrations of serum α_1-acid glycoprotein (α_1-AGP) in the smoking population. α_1-AGP is an acute phase reaction protein shown to play an important role in the plasma protein binding of cationic drugs (Piafsky et al 1978) including lidocaine (Piafsky & Knoppert 1979). However, in a multivariable study (Blain et al 1981) in which α_1-AGP was correlated with sex, age, smoking, and the use of contraceptive 'pill', smoking status had no influence on actual serum α_1-AGP concentrations. These observations prompted further investigation. The present communication supports the presence of elevated α_1-AGP levels in the serum of otherwise healthy smokers.

* Correspondence.

Methods

Subjects. Serum samples were obtained from 20 healthy, male volunteers, ten smokers and ten non-smokers. Smokers were classified as individuals who smoked more than one pack of cigarettes per day. Non-smokers were individuals who had not smoked for at least two years. The smoking and non-smoking groups were well matched for age (20–45 years old). All subjects were free of any disease or any medication known to cause changes in either serum α_1-AGP concentrations or drug binding to serum proteins. At the time of blood collection, a clinical chemistry profile was obtained using an automatic analyser.

Serum samples. Venous blood was collected in plastic syringes (preliminary studies indicated no influence of these syringes on drug binding) following an overnight fast. The blood was allowed to clot at room temperature for 2 h and then was centrifuged. The serum was collected and stored at −20 °C until used.

Protein binding studies. The serum protein binding of propranolol and phenytoin was determined by equilibrium dialysis using a dialysis membrane (Spectrapor No. 2, Spectrum Medical Industries, Los Angeles, CA) in 1 ml plexiglass cells (Bolab, Inc., Lake Havasu City, AZ). Propranolol and phenytoin were added, in separate volumetrics, to a buffer solution (0·134 M phosphate, pH 7·4) to achieve concentrations of 100 ng ml^{-1} and 15 μg ml^{-1}, respectively. A trace amount of tritiated drug ((±)-4-[^{3}H]propranolol hydrochloride, Amersham, Arlington Heights, IL or 5,5 [phenyl-4-[^{3}H](N)diphenylhydantoin], New England Nuclear, Boston, MA) was also added to the buffer solutions. Radiochemical purity of greater than 98% for both compounds was established by thin layer chromatography. Serum (1 ml) was dialysed in triplicate against