LETTER TO THE EDITOR

ROLE OF ADRENERGIC AND HISTAMINERGIC SYSTEMS IN CLONIDINE-INDUCED INHIBITION OF THE PINNAL REFLEX IN MICE*

Sir,

(Received on November 23, 1983)

Clonidine is reported to inhibit the α_2-adrenoceptor mediated pinnal reflex in mice (3). Clonidine produces its effect by acting as an α_2-adrenergic autoreceptor agonist (1). As such, clonidine is also agonist for presynaptic histamine H_2-receptors (8). To test whether the clonidine-induced inhibition of the pinnal reflex is mediated through adrenergic and/or histaminergic system, the interaction of agents influencing adrenergic and histaminergic systems was studied in experiments involving this reflex.

Swiss albino mice (20–30 g) of either sex were maintained in airconditioned room at 23±0.5°C and fed Gold Mohur HIND-LEVER diet and water *ad libitum*.

Experiments were always conducted between 10.00 and 12.00 hrs. The pinnal reflex was tested in animals given various pre-treatments and again at 30 min after ip injection of clonidine (400 *µg/kg*) as described by Witkin *et al.* (13). Response was considered to be present if it could be elicited bilaterally.

All the drugs were either dissolved in distilled water or suspended in 2% gum acacia, except 6-hydroxydopamine (6-HD) which was dissolved in artificial cerebrospinal fluid and administered into the cerebral ventricle through a cannula (2). Control groups received only the vehicle by corresponding routes. Statistical analysis was done using Chi_2 test (5).

Clonidine (100–500 *µg/kg*) produced a dose-dependent inhibitfon of pinnal reflex. ED_{50} was found to be 279.7±24.2 *µg/kg*. The peak effect was seen at 30 min and effect was over by 120 min. A 20% and 80% inhibition was recorded at 200 and 400 *µg/kg*, respectively. The latter dose was used in all subsequent work.

It will be seen (Table I) that none of the pre-treatments, *per se*, had any significant effect on pinnal reflex, while pre-treatment with reserpine, α-MPT, 6-HD, yohimbine and cimetidine significantly inhibited clonidine-induced pinnal reflex.

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TABLE I : Effects of agents influencing adrenergic and histaminergic systems in clonidine-induced inhibition of Pinnal reflex in mice.

Group	Treatment***	Dose* (*mg/kg*)	Given before	% inhibition of pinnal reflex
1.	Clonidine	0.4	30 min	80
2. i)	Reserpine	2.5	18 h	0
ii)	Reserpine + Clonidine			0[a]
3. i)	α-Methyl-p-tyrosine (MPT)	250.0	3 h	0
ii)	MPT + Clonidine			20[b]
iii)	6-Hydroxydopamine (6-HD)	0.05 icv**	72 h	0
iv)	6-HD + Clonidine			0[a]
4. i)	Phenoxybenzamine (PBZ)	5.0	1 h	0
ii)	PBZ + Clonidine			60[c]
iii)	Phentolamine	10.0	1 h	0
iv)	Phentolamine + Clonidine			60[c]
v)	Prazosin	5.0 sc.	30 min	0
vi)	Prazosin + Clonidine			70[c]
vii)	Yohimbine	2.5 sc.	45 min	0
viii)	Yohimbine + Clonidine			0[a]
ix)	Propranolol	1.0	30 min	0
x)	Propranolol + Clonidine			90[c]
5. i)	Haloperidol	0.25	45 min	0
ii)	Haloperidol + Clonidine			80[c]
6. i)	Mepyramine	10.0	30 min	0
ii)	Mepyramine + Clonidine			90[c]
iii)	Cimetidine	5.0	30 min	0
iv)	Cimetidine + Clonidine			20[b]

* All drugs have been given ip, unless otherwise mentioned.

** Total single dose.

*** Clonidine was given ip (0.4 *mg/kg*); pinnal reflex was tested 30 min later. Each group had 10 animals, except that group 3c, d had 5 and group 1 had 20 animals.

[a]$P < 0.001$, [b]$P < 0.01$, [c]$P > 0.05$ in comparison to group 1.

Clonidine has been shown to possess both peripheral and central actions (7). Clonidine is an agonist of presynaptic α-adrenoceptors (1). In the present study, clonidine

dose-dependently inhibited pinnal reflex and the peak effect was observed at 30 min which is in conformity with Brown and Handley (3).

Depletion of catecholamines as well as 5-hydroxytryptamine by reserpine pretreatment produced no effect on pinnal reflex. However, it completely blocked the clonidine-induced inhibition of the pinnal reflex indicating that either catecholamines and/or 5-hydroxytryptamine may be involved in the reflex. α-Methyl-p-tyrosine (10, 11), the catecholamine synthesis inhibitor which did not have its own effect on pinnal reflex, blocked the clonidine-induced inhibition of the pinnal reflex, indicating the involvement of catecholamines. Selective degeneration of paraventricular catecholaminergic neurone by 6-hydroxydopamine (6-HD) icv (12), completely blocked the inhibition of pinnal reflex by clonidine, whereas 6-HD *per se* did not have any effect. The results obtained with 6-HD strongly suggest that clonidine-induced inhibition of the pinnal reflex is central in origin and adrenergic neurones are involved, and also exclude the possibility of involvement of tryptaminergic neurones (4). Since, haloperidol itself had no effect nor it could block the clonidine-induced pinnal reflex inhibition, the involvement of dopaminergic system is also ruled out.

Phentolamine (presynaptic α-2 and postsynaptic α-1 antagonist), phenoxybenzamine (a strong postsynaptic α-1 and partial presynaptic α-2 antagonist (9) and prazosin (a specific α-1 antagonist (6), could not block the clonidine-induced inhibition of pinnal reflex, whereas, yohimbine (a selective presynaptic α-2 antagonist), completely blocked the clonidine action on pinnal reflex. This indicates involvement of pre-synaptic α-2 adrenoceptors.

Further, mepyramine (an H_1-antagonist) did not block the clonidine action on pinnal reflex, whereas cimetidine (an H_2-antagonist) completely blocked the clonidine-induced inhibition of pinnal reflex. This indicates involvement of H_2-receptors in clonidine action on pinnal reflex. Evidence that clonidine stimulates H_2-receptors in central nervous system is reported (8), and it is possible that in our work, the involved receptor could be H_2-type.

Thus, clonidine-induced inhibition of pinnal reflex is central in origin, and seems to involve both adrenergic and histaminergic systems. However, intact sympathetic system is required for clonidine action on pinnal reflex and this effect is blocked if presynaptic α_2-adrenoceptors and seemingly, presynaptic H_2-receptors are blocked.

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