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NEUROCHEMICAL ESTIMATIONS OF SOME NEW QUATERNARY PHENACYL-BROMOPIPERIDINIUM COMPOUNDS

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Considering the fact that N-alkyl substituted quaternary ammonium salts of piperidinium bromide induce brain catecholamine and indoleamine metabolism (Black *et al.,* 1986), we thought it may be valuable to investigate the effects of three selected phenacyl derivatives (I, V and VIII) of piperidine on brain monoamines metabolism in mice (100mg/kg body weight) assuming that these derivatives might alter the brain indoleamine and catecholamine levels differently. Studies are carried out by using HPLC technique. It was found that compound VIII possessed greater neuroleptic activity as compared to compounds I and V.

Keywords: Quaternary ammonium, catecholamine, indoleamine, neuroleptic activity, dopaminergic.

INTRODUCTION

Pethidine and piperidine-like compounds are well known for exhibiting agonistic as well as antagonistic activities. Molecular modifications of these compounds led to new opiates or narcotic analgesic (Janseen *et al,* 1986; Brown *et al*., 1998; Soukara *et al.,* 2001 and Sabine *et al*., 2003).

It is since two decades that much interest has been focused on the physiology and pharmacology of the dopamine (DA) autoreceptor agonists, for example, apomorphine, have shown to act preferentially on the autoreceptors thereby reducing nerve impulse flow, transmitter synthesis rate and release in the CNS (Bradbury *et al.,* 1983 and Baldessarini, 1984). Functionally stimulation of DA autoreceptors results in, among other things, a decrease in locomotor activity and exploratory behaviour (Baldessarini, 1996). It has been suggested previously that compounds with selective DA autoreceptor stimulating activity may be of therapeutic value (Foguet *et al.,* 1994; Mayer *et al.,* 2000; Thomas *et al*., 2003).

Hacksell *et al* (1981) synthesized and tested 30 compounds related to the selective dopamine autoreceptor agonists. Introduction of an additional hydroxyl group into 4-position of the aromatic ring gives a compound with dopaminergic activity but lacking selectivity for autoreceptor. In another work, Wikstrom *et al* (1984) described the synthesis and pharmacological evaluation of N-substituted propyl piperidine in order to examine their ability and interact with central dopamine (DA) receptors particularly DA autoreceptors. These compounds are found to be the most interesting compounds both from theoretical and therapeutic point of view.

Further investigations revealed that piperidine based analogs have been found effective in treating various neurological disorders (Michael *et al*., 1999; Barloco *et al*., 2001).

In the possible concern that these newly synthesized derivatives of piperidine may have some toxic effects on dopaminergic neurons and monoamines, present study has been carried out.

MATERIALS AND METHODS

Animals

Male albino mice (locally bred) weighing 25-30g were housed individually in the same environmental conditions for about four days before experimentation.

Drugs

Synthetic derivatives of piperidine used as drugs were:

1 1-Methyl-l (4′-methoxy) phenacyl-4-hydroxy piperidinium bromide (I).
2 1-Methyl-l (4′-nitro) phenacyl-4-hydroxy piperidinium bromide (V).
3 1-Methyl-l (4′-methyl) phenacyl-4-hydroxy piperidinium bromide (VIII).

These synthetic derivatives were dissolved in saline and injected to the test animals (i.p) at the doses of 100mg/kg body weight. Pethidine and saline were injected to the standard and control animals by the same route.

Extraction and estimation procedure

Animals were killed 1 hour after the injection of saline, standard and test compounds. Brain was taken out within 1 minute, stored at 70^{o}C and samples were extracted following the procedure described earlier in the thesis (Shahnaz, 1997). Brain concentrations of DA, DOPAC and HVA were determined by HPLC-EC method at 0.8V electrode potential (Haleem *et al.*, 1990).

Statistical analysis

Data were analysed by one-way ANOVA. Post-hoc comparisons were done by Neman-keuls test. Differences were considered significant when $P<0.01$ from control.

Table
Effects of phenacyl-bromopiperdinium compounds (I, V and VIII) on the release of neurochemical transmitters (ng/g) in mice brain 1 hour after the injection

Neurotransmitter/ Metabolites	Control (water for injection)	Compounds			ANOVA Diff. 4,25	
		I	V	VIII	F	P
DA	119 ± 38	140 ± 64	406 ± 80	818 ± 43	0.78	P<0.01
DOPAC	192 ± 62	241 ± 72	135 ± 78	513 ± 73	1.3	P≤0.01
HVA	73 ± 38	141 ± 15	111 ± 21	117 ± 11	0.82	P<0.01
5-HT	88 ± 22	16 ± 7	42 ± 13	59 ± 19	1.3	P≤0.01
5-HIAA	117 ± 39	28.5 ± 32	390 ± 38	157 ± 42	0.36	P<0.01

Values are mean ± S.D. (n=5). Difference significant by Newman-Keuls tests were P<0.01 from control following one-way ANOVA.

RESULTS

Results of effects of three substituted 1-phenacyl-4-hydroxyl-4-phenyl piperidines (I, V and VIII) on mice brain monoamines levels depicted in the table with representative figures are given as under:

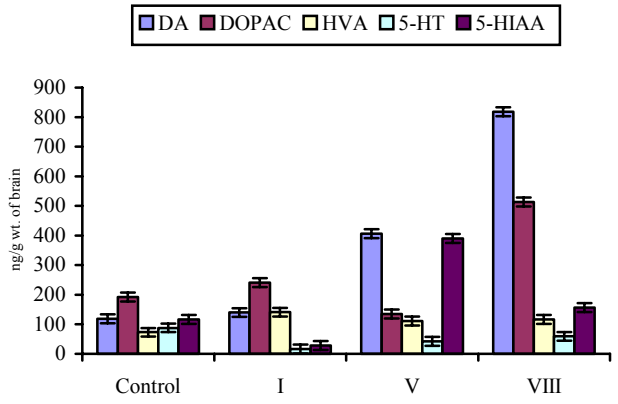

Fig. Effect of phenacyl-bromopiperidine derivatives (I, V, VIII) on the release of neurochemical transmitters (ng/g) in mice brain 1 hour after the injection.

(Values are mean ± S.D. (n=5). Difference significant by Newman-Keuls tests were P<0.01 from control following one-way ANOVA).

Figure shows that the DA levels were increased significantly by compound (V) and (VIII) while derivative (I) did not produce any significant change in the brain DA levels.

The concentrations of DOPAC is increased considerably by the compounds I and VIII while compound V has decreased the DOPAC concentration.

The figure also reveals that HVA concentrations are markedly increased by the administration of all these compounds.

As far as 5-HT and 5-HIAA concentrations are concerned, these all derivatives decreased the concentration of 5-HT remarkably and enhanced the concentration of 5-HIAA considerably except compound I which has decreased it to a greater extent.

DISCUSSION

Considering the fact on the basis of literature, that substituted phenacyl derivatives of piperidine induce brain catecholamine and indoleamine metabolism (Black and Brandt, 1986), it was profound importance to investigate three newly synthesized derivatives of piperidine (I, V and VIII) on brain dopamine and indoleamine in mice assuming that these derivatives might alter them.

Results shown in table and figure revealed enhancement of DA levels by the administration of all these three derivatives. The increase in DA metabolism may possibly occur because of DA antagonistic activity. Therefore, this study suggests that these compounds may have neuroleptic like effects (Capunano *et al*., 2002). This is also shown from the figure that these compounds have enhanced the levels of DOPAC and HVA except 4-nitro moiety (V) which caused decrease in DOPAC level.

The enhancement of both DA and its metabolites DOPAC and HVA following the administration of these derivatives suggest increase turnover of DA due to an increase in the activity of particularly rate-limiting catecholamine synthesizing enzyme tyrosine hydroxylase (Sved *et al*., 1981).

As evident from the figure 5-HT level is decreased by these derivatives, levels are increased by V and VIII while compound I, has decreased it to a greater extent. Increased level of 5-HIAA is suggesting that the administration of compound V and VIII may increase 5-HT turnover in the brain (Ross *et al.,* 1986). A role of indoleamine in the antinociceptive effects of morphine is often described in animal studies (Samanin *et al.,* 1978). The present study shows that administration of piperidine derivatives increase

brain serotonin metabolism. This may occur because of an increase in the availability of enzyme tryptophan hydroxylase (Schaechter and Wurtsman, 1990).

CONCLUSION

The present study suggests that these compounds (I, V and VIII) may be carefully used as drugs in psychotic patients because of their effects on the enhancement of both serotonin and catecholamine metabolism.

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