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Desensitization of β-adrenoceptors following repeated injections of 2-substituted 4-phenylquinolines*

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The chronic effects of five 2-substituted 4-phenylquinoline derivatives on the sensitivity of the noradrenergic cyclic AMP-generating system in the rat brain cortex have been determined, and compared with those of the typical and atypical antidepressants imipramine and trazodone, respectively. Acute treatment (single i.p. dose of 20 mg kg^{-1}) and sub-chronic treatment (20 mg kg^{-1} daily for 10 days) induced no significant desensitization of the β-adrenoceptors. However, chronic treatment (20 mg kg^{-1} daily for 3 weeks) significantly decreased the isoprenaline-induced increase in cyclic AMP, suggesting desensitization. This effect, coupled with previous findings, points to a potential role of these compounds as antidepressants.

Pharmacotherapy treatment of endogenous depression usually requires three to four weeks of continuing drug administration to achieve any therapeutic response.

Petty et al (1982) observed rapid reversal of the depressed behaviour of rats after injection of imipramine directly into the anterior neocortex; this led them to suggest that the delayed onset of therapeutic action of antidepressant drugs is due to the time required to achieve adequate drug levels at the sites of action. If this is true, modifications of physicochemical parameters such as lipophilicity, molecular size, and electronic characteristics of antidepressants, could play a significant role in achieving the required concentration of drugs at their site(s) of action. With this in mind, we have previously synthesized eleven new derivatives of 4-phenylquinoline which demonstrated antidepressant potential as revealed by their antagonism to reserpine-induced hypothermia in mice (Alhaider et al 1985) and inhibition of the uptake of [^{3}H]noradrenaline and [^{3}H]5-hydroxytryptamine into brain synaptosomal preparations (Alhaider 1984). Also, some of these drugs were less potent compared with imipramine in their antihistaminic, anticholinergic, and cardiovascular side effects (Alhaider 1986).

We set out to determine whether these compounds are superior to conventional antidepressants in achieving a higher concentration at the site(s) of action. To assess this, we used the isoprenaline-stimulated adenyl cyclase system in rat brain to measure the sensitivity of β-adrenoceptors. Vetulani & Sulser (1975) have reported that the sensitivity of this sytem is diminished by chronic administration of antidepressants such as desipramine and iprindole. Thus, we have tested the ability of our new compounds to induce desensitization of the β-adrenoceptors, and compared this desensitization with that induced by imipramine and trazodone.

Materials and methods

Compounds I 1-(4-phenyl-2-quinolyl)-2,2-dimethylethylenediamine; II, 4-phenyl-2-[2,2-(dimethylamino)-ethoxy]quinoline; III, 1-(4-phenyl-2-quinolyl)piperazine; IV, 4-(ω-chloropropyl)-1-(4-phenyl-2-quinolyl)-piperazine; and V, 2-[3[4[2-(4-phenylquinolyl)]-1-piperazinyl]propyl]-1,2,4-triazolo [4, 3-*a*] pyridine-3 [2*H*] one were prepared according to Alhaider et al (1985) and used as their hydrochlorides. Imipramine (Tofranil) and trazodone (Desyrel) were kindly donated by Ciba-Geigy, and Mead Johnson Pharmaceutical Division, respectively. Isoprenaline HCl and aminophylline were obtained from commercial sources. c-AMP kits were purchased from Amersham.

Drug doses reported were based on the weights of the salt supplied.

Male Wistar rats (initial weight 170–200 g) were obtained from the animal house of King Saud University and housed in groups of five under standard laboratory conditions. Treatment was carried out once daily. All drugs were injected intraperitoneally (20 mg kg^{-1}), control rats receiving a corresponding volume of vehicle. After certain intervals of treatment, rats were decapitated and cerebral cortical slices were dissected as rapidly as possible and suspended in oxygenated Krebs-bicarbonate buffer (pH 7·4). Slices were preincubated for 60 min in a shaking water bath at 37 °C with two changes of medium. Slices weighing 50–100 mg were placed in tubes containing 200 μL of fresh Krebs-bicarbonate buffer and 50 μL of 2 mM aminophylline, and chopped with scissors.

The incubation was started by the addition of 50 μL of 120 mM isoprenaline hydrochloride and the reaction mixture was oxygenated with 5% CO_2 in oxygen. The test tubes were incubated for 15 min at 37 °C and the reaction was then terminated by boiling for 10 min. Duplicate 50 μL samples of the extract were assayed for cyclic (c)AMP content by a kit method (Amersham). All values were corrected for recoveries and cAMP was expressed in pmol mg^{-1} of wet tissue. Student's two-tailed *t*-test was used for statistical comparisons of results.

* Part of this work was presented as a poster at the FASEB meeting in St. Louis Mo., April, 1985.

Results and discussion

Table 1 shows the effect of compounds I–V, imipramine, and trazodone on the isoprenaline-induced response of rat cerebral cortex cAMP levels after specified intervals of treatment. Results are presented as mean ± s.e.m. (n = 5).

Table 1. Effect of imipramine, trazodone, and 4-phenylquinoline derivatives on isoprenaline-stimulated formation of cAMP of rat cerebral cortex.

Treatment	Duration of treatment (days)	cAMP (pmol mg^{-1} wet tissue) ± s.e.m. (n = 5)	% of control response
Vehicle	1	126·01 ± 7·48	100
	10	123·00 ± 5·02	100
	21	125·71 ± 6·75	100
Imipramine	1	128·21 ± 5·01	100
	10	93·01 ± 5·53	76
	21	26·71 ± 2·37	21
Trazodone	1	122·12 ± 5·19	100
	10	116·36 ± 5·60	95
	21	61·57 ± 2·89	49
I	1	130·00 ± 4·69	100
	10	95·81 ± 3·79	78
	21	13·18 ± 1·52	11
II	1	124·94 ± 4·88	100
	10	101·10 ± 3·97	82
	21	14·43 ± 1·21	12
III	1	126·21 ± 5·37	100
	10	87·32 ± 5·68	71
	21	11·53 ± 1·18	8
IV	1	123·21 ± 5·47	100
	10	88·01 ± 4·49	72
	21	20·10 ± 1·68	16
V	1	119·30 ± 5·07	100
	10	89·11 ± 4·58	72
	21	14·78 ± 1·28	12

As shown in Table 1, prolonged treatment with the typical antidepressant imipramine, the atypical trazodone and the 4-phenyl quinoline derivatives decreased the isoprenaline-induced effect on cAMP by 50–90% compared with the control. All decreases were significant ($P < 0·05$, n = 5). In contrast, all drugs tested induced a much lower decrease in sensitivity after subchronic treatment for 10 days, and in every case, this decrease was not significant ($P > 0·05$, n = 5).

The results thus clearly show that the new 4-phenylquinoline derivatives share with established antidepressants the property of desensitization of β-adrenoceptors after chronic treatment. We have previously shown that these compounds also have other pharmacological and biochemical properties in common with the established antidepressants (e.g., imipramine and trazodone). This evidence suggests potential antidepressant activity of these new compounds.

However, the new compounds tested were no better in desensitizing β-receptors, despite their different lipophilicities, and hence the potential to cross the blood brain barrier. Their apparent partition coefficients were in the range of 0·98–2·26 while those of imipramine and trazodone are 1·48 and 0·76, respectively (Alhaider 1984). This suggests that either the kind of structural modification employed is not the appropriate one, or that pharmacodynamic factors such as receptor specificities may play a more important role in determining the lag period required between initiation of treatment and the appearance of clinical response. It, also seems likely that the continued presence of the drug is required to mediate β-receptor desensitization. To establish whether the delayed onset of therapeutic action associated with pharmacotherapy of antidepressants is due mainly to the time required to achieve adequate drug levels at the site(s) of action, it may be necessary to measure the sensitivity of β-adrenoceptors after short treatment by microinjection of therapeutic doses of imipramine directly at the anterior neocortex. Furthermore, a subacute co-administration of antidepressant drugs with different neurochemical effects may produce a fast desensitization of β-adrenoceptors.

In conclusion, the present work has revealed that chronic treatment with 4-phenylquinoline derivatives significantly decreased isoprenaline-induced increases in cAMP in the rat cerebral cortex. This points to a potential role for these compounds as antidepressant candidates.

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