Tricyclic Antidepressants: Therapeutic Properties and Affinity for α-Noradrenergic Receptor Binding Sites in the Brain

Abstract. *Tricyclic antidepressants vary in their capacity to cause psychomotor activation, to relieve agitated depressive states, and to cause sedation and hypotension. We have quantified relative potencies of tricyclic antidepressants in competing for the binding of ^{3}H-labeled WB-4101 to α-noradrenergic receptor sites in rat brain membranes. Affinities of tricyclic drugs for α-noradrenergic receptor sites in the brain correlate well with the capacity of these agents to relieve psychomotor agitation and to induce sedation and hypotension; these affinities also correlate inversely with tendencies to elicit psychomotor activation.*

Tricyclic antidepressants, the major agents used in treating depression, vary considerably in their therapeutic properties. Tertiary amine tricyclics are particularly effective in patients with psychomotor agitation and also elicit the highest incidence of sedative and hypotensive side effects, whereas the secondary amines are more effective in retarded depression since they produce psychomotor activation and are less likely to elicit sedative and hypotensive side effects (*1–4*). Since the tertiary amine tricyclics are more potent inhibitors of serotonin uptake than the secondary amines, while the reverse is true for the inhibition of norepinephrine uptake, some investigators have suggested that psychomotor activation by tricyclic antidepressants results from blockade of norepinephrine uptake in the central nervous system, while reduction of agitation is attributable to inhibition of serotonin uptake (*4–7*).

α-Noradrenergic receptor sites in the brain can be labeled with several tritiated drugs (*8, 9*). The sedative-hypotensive actions of neuroleptics are predicted by their affinities for α-receptors, suggesting that these agents cause sedation and hypotension by blocking α-noradrenergic receptors (*10*). We now report a close correlation between the ability of tricyclic antidepressants to reduce psychomotor agitation and their affinities for α-noradrenergic binding sites in brain membranes.

α-Receptor binding assays with ^{3}H-labeled WB-4101 (2-([2′,6′-dimethoxy]-phenoxyethylamino) methylbenzodioxan), a potent α-adrenergic antagonist, were performed essentially as described (*9*). Homogenates (Brinkmann Polytron) of fresh rat whole brain excluding the cerebellum in tris-HCl buffer were washed twice by centrifugation, and then suspended in 50 volumes of cold 50 m*M* tris-HCl buffer, *p*H 7.7, at 25°C. For binding assays, each tube received 1.0 ml of membrane suspension (20 mg, wet weight), 0.2 n*M* [^{3}H]WB-4101 (11.7 c/mmole; custom tritiated, New England Nuclear, more than 95 percent pure) and various concentrations of nonradioactive drugs. The incubation volume in each tube was brought to 2 ml with cold 50 m*M* tris-HCl buffer, *p*H 7.7, at 25°C. Triplicate tubes were incubated at 25°C for 20 minutes and rapidly filtered under vacuum through Whatman GF/B filters with two 5-ml rinses of cold buffer. The filters were counted by liquid scintillation spectrometry in 10 ml of Formula 947 (New England Nuclear) at 37 percent efficiency.

Specific binding of [^{3}H]WB-4101 was measured as the excess over blanks taken in the presence of 100 μ*M* (−)-norepinephrine. Under these conditions, specific binding (600 to 700 count/min) constituted two-thirds of the total binding. Specific binding of [^{3}H]WB-4101 to rat brain membranes is saturable, with a dissociation constant (K_D) of about 0.5 n*M*.

The tertiary amine tricyclics in general are more potent than the secondary amines in competing for [^{3}H]WB-4101 binding to α-noradrenergic receptors (Table 1). Among the tertiary amines, doxepin and amitriptyline are equally potent and about 2.5 times more potent than chlorimipramine and imipramine. With apparent inhibition constant (K_i) values of 23 to 24 n*M*, doxepin and amitriptyline are only six times weaker than the potent classical α-receptor antagonists phentolamine and phenoxybenzamine (*9*). The secondary amines are only one-third as potent as the corresponding tertiary amines in competing for [^{3}H]WB-4101 binding. The tertiary amine tricyclics are substantially more potent in competing for α-receptor binding than in blocking norepinephrine and serotonin uptake in brain slices and synaptosomes (*6*).

The secondary amine tricyclics, especially desipramine and protriptyline, tend to cause psychomotor activation in patients and are particularly useful in treating retarded depression, whereas the tertiary amines, with the possible exception of imipramine, cause little psychomotor activation (*2, 3, 7*). The relative psychomotor activating effects of these drugs correlate inversely with their potency in competing for α-noradrenergic binding sites since desipramine and protriptyline are the weakest α-blockers and the tertiary amines are substantially more active. Tricyclic drugs that fail to cause psychomotor activation are more sedating and have greater therapeutic utility in relieving the psychomotor agitation of depressed patients (*2*).

Although it is difficult to distinguish rigorously between the relative activities of these drugs in eliciting particular clinical effects, some quantitative evaluations have been performed (*2*). For six tricyclic antidepressants, selective therapeutic efficacies for depressive psychomotor agitation versus psychomotor inhibition correlate well with affinities for α-noradrenergic binding sites (*11*) (Fig. 1). Inhibition by these drugs of the arousal reaction in rabbits after electrical stimulation of the midbrain reticular formation provides an animal model for clinical reduction of psychomotor agitation (*2*). The rank-order of potencies of tricyclic drugs in eliciting this effect parallels their affinities for α-receptor sites with a correlation coefficient of .94 ($P < .05$) (Table 1).

Earlier we demonstrated that the binding to brain membranes of [^{3}H]WB-4101

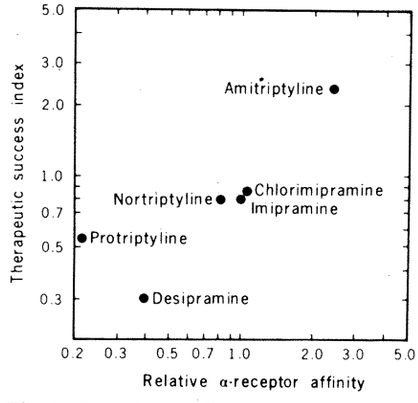

Fig. 1. Tricyclic antidepressants: correlation between affinities for [^{3}H]WB-4101 α-noradrenergic binding sites in the rat brain, and relative therapeutic efficacies in relief of depressions with psychomotor agitation compared to relief of depressions with psychomotor inhibition, calculated from available data (*2, 11*). The α-receptor affinity values were calculated from the reciprocals of the K_i values shown in Table 1, giving imipramine an arbitrary affinity value of 1.0. The correlation coefficient $r = .84$ is significant at $P < .05$. If protriptyline, which, unlike the other tricyclic antidepressants in the figure, is lacking a middle ring, is excluded, the correlation coefficient $r = .99$ is significant at $P < .001$, and the slope is 1.1. The therapeutic success index is defined in (*11*).

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Table 1. Tricyclic antidepressants: comparison of affinities for [^{3}H]WB-4101 binding sites with in vivo pharmacological properties. For each drug, inhibition of [^{3}H]WB-4101 binding was measured at three to six concentrations, and the median inhibition concentrations (IC_{50}) were determined by log-probit analysis. These were converted to apparent K_i values by the equation $K_i = IC_{50}/[1 + ([^3H]WB\text{-}4101)]/K_D$, where K_D is the dissociation constant of [^{3}H]WB-4101, 0.5 n*M*. Each value is the mean ± standard error of four experiments, each conducted in triplicate. The qualitative data in columns 2 and 3 were derived from reviews of clinical and animal studies (*1–4, 7, 14*). In animals, sedation and psychomotor activation were measured in terms of alteration of barbiturate-induced sleep, cortical electroencephalogram, spontaneous motor activity, and drowsiness; hypotensive potential was demonstrated as decreases in blood pressure and heart rate after systemic administration, and as blocking ability in isolated aortic and papillary muscle preparations. Clinical data correlate reduction in insomnia and agitation, and general hypnotic effects, with sedative potential, increased restlessness with psychomotor activation, and incidence of orthostatic hypotension with hypotensive potential. The lack of quantitative data obtained in the same experimental conditions over the spectrum of antidepressants did not permit statistical weighing of the data for averaging, and hence quantitative comparisons could not be made. The data in column 4 for six antidepressant drugs were obtained from Poeldinger (*2*); they represent the relative doses of drugs (amitriptyline = 1.0) needed to raise the threshold of the arousal reaction in the rabbit, after electrical stimulation of the mesencephalic reticular formation, to 150 percent of control value.

Drug	Inhibition of [^{3}H]WB-4101 binding, K_i (n*M*)	Ability to cause psychomotor activation	Sedative and hypotensive properties	Ability to increase arousal threshold in rabbits
		Tertiary amines		
Doxepin	23 ± 5	−	++	
Amitriptyline	24 ± 4	−	++	1.0
Chlorimipramine	55 ± 11	−	+	1.1
Imipramine	58 ± 5	+	+	1.2
		Secondary amines		
Nortriptyline	71 ± 10	++	+	1.3
Desipramine	148 ± 18	+++	−	> 2.0
Protriptyline	277 ± 24	+++	−	2.0

represents a specific association with α-noradrenergic receptor sites (*9*). The suggestion that the effects of the tricyclic antidepressant drugs on these binding sites represents blockade of functional α-receptors is supported by findings that the tertiary amine tricyclic drugs are more potent than the secondary amine drugs in blocking norepinephrine stimulation of cyclic AMP (adenosine 3′5′-monophosphate) accumulation in slices of rat cerebral cortex (*12*).

To explain different therapeutic effects of various tricyclic antidepressants it has been suggested that secondary amines such as desipramine and protriptyline elicit psychomotor activation and enhance "drive" by blocking norepinephrine uptake, while tertiary amines selectively elevate mood by inhibiting neuronal uptake of serotonin (*4–7*). According to this model the anti-agitation actions of the tertiary amines are presumably associated with inhibition of serotonin uptake. Alternatively, the intrinsic antidepressant efficacies of all the tricyclic drugs may be similar and related to inhibition of neuronal uptake of one or another (or both) of the biogenic amines. Differential effects on psychomotor agitation and sedation-hypotension may be related to relative α-noradrenergic blocking actions. In the absence of α-noradrenergic blocking activity, all the tricyclic antidepressants may cause a similar degree of psychomotor activation. However, the α-blocking properties of the tertiary amines would counteract such effects and also confer a capacity to relieve agitation and to cause sedation and hypotension. The differential effects of tertiary and secondary amine tricyclics may be modified to a certain extent because of demethylation of the tertiary amine drugs, which occurs to a certain extent in most patients. The relative specificity of the tricyclic antidepressants as α-receptor antagonists is indicated by the fact that they are about 3000-fold weaker inhibitors of the binding of dopamine and β-adrenergic ligands, respectively (*13*).

Certain neuroleptics are even more active in eliciting sedation and hypotension than the tertiary amine tricyclics. Earlier we observed a close association between the relative sedative-hypotensive actions of neuroleptics and their affinities for α-noradrenergic receptor binding sites labeled with [^{3}H]WB-4101 (*10*). The neuroleptics with greatest sedative properties are substantially more potent in their effects on α-noradrenergic receptor sites than any of the tricyclic drugs examined there (*10*). Interestingly, thioridazine, a phenothiazine neuroleptic whose relative α-noradrenergic blocking activity is among the greatest of all neuroleptics examined (*10*), is efficacious in relieving agitated depression (*2*). It is possible that its utility in treating agitated depression may derive from α-noradrenergic blocking effects in the brain and may therefore represent a mechanism of action similar to that of the anti-agitation actions of tertiary amine tricyclic antidepressants such as amitriptyline and doxepin.

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11. The therapeutic efficacies, derived from clinical studies of 40 to 100 patients taking each individual antidepressant (*2*), are based on the proportion of therapeutic successes for each drug in the two depressive syndromes—agitated depression and retarded depression. The ratio figure for each drug, obtained by dividing the proportionate, or percent, success in treating patients with agitated depression, by the proportionate, or percent, success in treating patients with retarded depression, is called the "therapeutic success index" for that particular drug. A drug with an index of 3.0 would be three times more successful in treating patients with agitated depression than in treating patients with retarded depression.
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