Serotonergic and Noradrenergic Reuptake Inhibitors: Prediction of Clinical Effects From In Vitro Potencies

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This article reviews the pharmacology of antidepressants, particularly focusing on those that act acutely by blocking the reuptake of norepinephrine (NE) and/or serotonin (5-HT). Such drugs have a very wide range of potencies, measured in vitro, to inhibit the reuptake of these biogenic amines. As a group, the selective serotonin reuptake inhibitors (SSRIs) are the most potent at inhibiting the reuptake of 5-HT. Some tricyclic antidepressants (TCAs), such as desipramine and nortriptyline, are much more potent at blocking NE reuptake than 5-HT reuptake, as is the new non-TCA drug reboxetine. Among SSRIs, paroxetine is most potent at blocking the reuptake of NE. When considering whether such potencies measured in vitro translate into pharmacologic effects clinically, it is necessary to know how much drug gets to its site of therapeutic action, presumably the brain. Most, but not all, antidepressants are extensively bound to plasma proteins, and this binding limits considerably the penetration of these drugs across the blood-brain barrier. The amount of drug present in the extracellular fluid (ECF) of brain approximates the non–protein-bound drug concentration in plasma. Comparison of the concentration of antidepressants in ECF with their potencies to inhibit the reuptake of 5-HT and/or NE reveals why some drugs block the reuptake of these biogenic amines in either a selective or nonselective manner. This analysis reveals that venlafaxine may be unique among antidepressants in having a dose-dependent nonselectivity; at low doses it acts primarily as an SSRI, but at higher doses it inhibits the reuptake of NE as well. *(J Clin Psychiatry 2001;62[suppl 12]:16–23)*

This article reviews the pharmacology of several antidepressants, particularly focusing on the potencies of those that act by acutely blocking norepinephrine (NE) or serotonin (5-HT) reuptake. The reason for this focus is that the "trigger" for the antidepressant and/or the anxiolytic effects of these drugs is their effects on NE or 5-HT. The behavioral improvement may not be the direct result of enhancement of noradrenergic or serotonergic transmission caused by reuptake inhibition, but rather the indirect downstream effects triggered or initiated by that enhancement.[1–3] Currently, though, the path to such downstream effectors is through NE or 5-HT. The question of how antidepressants can be anxiolytic can be modified to ask how enhancement of noradrenergic or serotonergic transmission could produce an anxiolytic effect. To address this,

the behavioral roles of 5-HT and NE will be reviewed briefly as well. Presently, though, we cannot answer this question definitively.

PROPOSED ANTIDEPRESSANT CATEGORIES

Antidepressants may be grouped on the basis of their acute pharmacologic effects that are presumed to initiate behavioral improvement. If this grouping is done, 4 categories of antidepressants result (Table 1). The first category includes drugs that selectively enhance the effects of NE, primarily through reuptake inhibition. Such drugs include certain tricyclic antidepressants (TCAs) and TCA-like compounds (maprotiline). Another drug that falls into this category is reboxetine, although it is distinct structurally from the TCAs and TCA-like compounds.[5] It is currently available as an antidepressant in European and South American countries but is not yet marketed in the United States. The second category is the selective serotonin reuptake inhibitors (SSRI), which, as their class name implies, selectively block the reuptake of 5-HT in vivo. The third category comprises drugs that act nonselectively on noradrenergic and serotonergic neurons to cause enhancement of synaptic transmission. Monoamine oxidase inhibitors are in this category, as are some TCAs. There are also some novel drugs in this category. One is venlafaxine, which will be discussed in more detail later, and another is

Table 1. Proposed Classification for Antidepressants Based on Presumed Mechanisms of Action[a]

Proposed Classification	Drug Name	Current Classification (if any)
Selective enhancement of NE effects	Desipramine, nortriptyline, protriptyline	TCAs
	Amoxapine, maprotiline	TCA-like
	Reboxetine	...
Selective enhancement of 5-HT effects	Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	SSRIs
Nonselective enhancement of NE and 5-HT effects	Amitriptyline, imipramine	TCAs
	Phenelzine, tranylcypromine	MAOIs
	Mirtazapine	...
	Venlafaxine	SSRI[b]
Unknown potent stimulatory effects on NE or 5-HT	Trimipramine	TCA
	Bupropion	...
	Nefazodone	...
	Trazodone	...

[a]Adapted, with permission, from Frazer.[4] Abbreviations: 5-HT = serotonin, MAOI = monoamine oxidase inhibitor, NE = norepinephrine, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.
[b]Becomes nonselective at higher doses.

mirtazapine. Mirtazapine is not a potent inhibitor of the reuptake of either NE or 5-HT,[6] but it is a relatively potent antagonist of inhibitory α_2-autoreceptors on noradrenergic nerves. By blocking such autoreceptors, mirtazapine removes their inhibitory influence on noradrenergic transmission. Mirtazapine can directly enhance NE-mediated transmission by this mechanism.[7,8] In this respect, then, it might be appropriate to place mirtazapine in the first category. However, mirtazapine may also enhance serotonergic transmission, albeit indirectly.[9–11] This enhancement is caused in part by the activation by NE of α_1-noradrenergic receptors located on serotonergic soma and dendrites to increase cell firing and the release of 5-HT.[12] Mirtazapine may also block inhibitory α_2-adrenoceptors located on serotonergic terminals, i.e., heteroreceptors.[7,13] Some recent data question the likelihood that mirtazapine enhances serotonergic transmission.[14] Whether mirtazapine increases serotonergic transmission may depend on the state of activation of the central noradrenergic system when mirtazapine is administered. Further research is needed to clarify this issue. At this time, though, mirtazapine has been placed in the third category.

The fourth category comprises a heterogeneous group of drugs that do not have known potent, acute pharmacologic effects that would result in enhancement of noradrenergic and/or serotonergic transmission. In other words, their mechanisms of action are unknown. Drugs in this category include the TCA trimipramine as well as bupropion, nefazodone, and trazodone. Bupropion has been speculated to act through dopaminergic mechanisms, since it is the only antidepressant that more potently blocks the reuptake of dopamine than the reuptake of either NE or 5-HT.[15] However, bupropion and its metabo-

lites are very weak inhibitors of the reuptake of all 3 biogenic amines, with potencies in the micromolar range.[15] The most potent acute effect of nefazodone and trazodone on serotonergic or noradrenergic systems is their antagonism of $5-HT_{2A}$ receptors.[16] They are very weak inhibitors of NE reuptake and relatively weak as inhibitors of 5-HT reuptake, as well.[17] Thus, acute pharmacologic properties that contribute to the efficacy of the drugs in the fourth category remain unknown.

As indicated, then, although there are different ways in which antidepressants can enhance noradrenergic and/or serotonergic transmission, the great majority of these drugs do so by blocking the reuptake of NE and/or 5-HT. Reuptake of these biogenic amines is due to the activity of specific transporter proteins located in the plasma membrane.[18,19] The reuptake of 5-HT occurs through activity of the 5-HT transporter, whereas the NE transporter mediates the reuptake of NE. These cellular proteins are the key initial targets for many antidepressants. They have been the subject of much research that originally dealt with the potencies of antidepressants to inhibit acutely the reuptake of radioactive 5-HT or NE into preparations of brain homogenates or synaptosomal preparations or slices of brain tissue, usually of rats. More recently, the potencies of these drugs to inhibit the binding of radioactive ligands to these transporters have been measured.[20]

IN VITRO POTENCIES TO INHIBIT REUPTAKE

The potencies of many antidepressants to inhibit the uptake of [^{3}H]5-HT into rat brain homogenates are shown in Figure 1. Potencies are shown as IC_{50} values, which refers to the concentration of drug needed to inhibit uptake by 50%. This is a standard way to compare the potencies of different drugs. IC_{50} is an experimentally determined value. Its value depends on the concentration of radioactive compound (e.g., 5-HT or NE) used. Because antidepressants are competitive inhibitors of uptake, the higher the concentration of radioactive material used, the larger the IC_{50} value of the drug will be. K_i value, the inhibitory constant, is the concentration of drug needed to occupy 50% of transporters or receptors and is independent of the concentration of radioactive compound used. K_i values, therefore, have also been used to compare the interactions of antidepressants with monoamine transporters. The relationship between K_i values and IC_{50} values is given by the equation $K_i = IC_{50} / 1 + (L/K_m)$, where L is the concentration of radioactive compound ([^{3}H]5-HT or [^{3}H]NE) used in the experiment and K_m is the affinity of the radioactive compound for its transporter. K_i values are useful when comparing potencies of drugs obtained by different investigators who used different concentrations of radioactive agent (e.g., [^{3}H]NE).
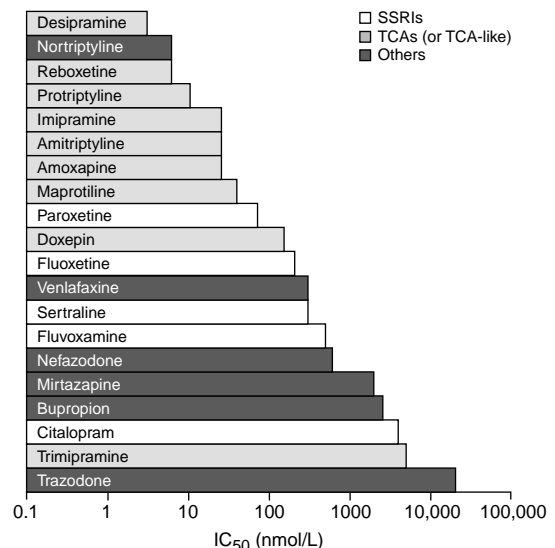
Irrespective of whether IC_{50} or K_i values are used, the lower the number (in Figure 1, the shorter the bar), the more potent the drug. So, for example, the most potent

Figure 1. Potency of Antidepressants to Inhibit
5-HT Reuptake[a]
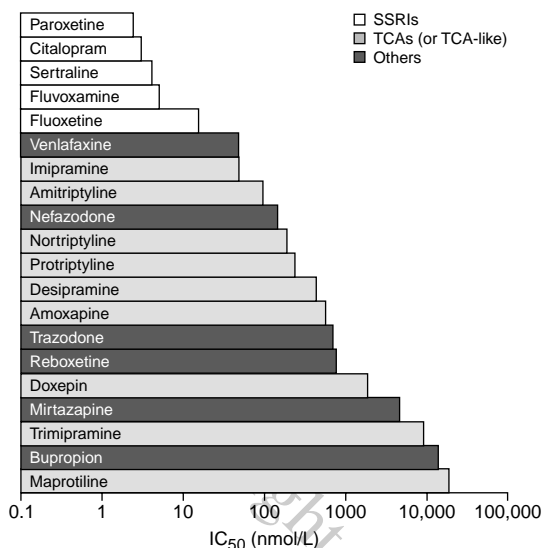
Figure 2. Potency of Antidepressants to Inhibit NE Reuptake[a]

[a]Adapted, with permission, from Frazer.[4] Data from Wong et al.,[5] Bolden-Watson and Richelson,[17] Hyttel,[21] Hyttel and Larsen,[22] and Richelson.[23] Abbreviations: 5-HT = serotonin, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant. Some values have been adjusted to reflect not only the absolute potencies of the drugs in blocking the reuptake of 5-HT but also their relative potencies in relationship to each other.

[a]Adapted, with permission, from Frazer.[4] Data from Wong et al.,[5] Bolden-Watson and Richelson,[17] Hyttel,[21] Hyttel and Larsen,[22] and Richelson.[23] Abbreviations: NE = norepinephrine, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant. Some values have been adjusted to reflect not only the absolute potencies of the drugs in blocking the reuptake of NE but also their relative potencies in relationship to each other.

antidepressant to inhibit 5-HT reuptake in Figure 1 is paroxetine; it blocks or occupies 50% of 5-HT transporters at a concentration of about 1 nmol/L. To obtain an equivalent degree of blockade of 5-HT uptake with the drug maprotiline, it takes about 20,000 nmol/L. Paroxetine, then, is about 20,000 times more potent at inhibiting 5-HT uptake than maprotiline. Antidepressants have a large range of potencies to inhibit 5-HT reuptake. The SSRIs as a group are understandably quite potent, and some TCAs have reasonably good potency, whereas drugs such as trimipramine, bupropion, and maprotiline are quite weak.

The picture is the same for [3H]NE reuptake into rat brain homogenates, but the rank order of the drugs is quite different (Figure 2). Here, TCAs and reboxetine are quite potent, with the SSRIs being less potent. Among the SSRIs, paroxetine is the most potent at blocking NE uptake, whereas citalopram is the least potent. Some drugs that are very weak at blocking 5-HT uptake, e.g., trimipramine and bupropion, are also very weak at blocking NE reuptake.

When antidepressants have potencies in vitro of about 10 nmol/L or less, there is a very strong likelihood that the pharmacologic effect is going to occur clinically. I will describe why this is so later. By contrast, when the potencies are 1000 nmol/L or greater, the likelihood is that the pharmacologic effect is not going to occur clinically, or if it does, will not have much consequence. When the potencies are between these values, it is more difficult to predict if the effect occurs clinically.

ANTIDEPRESSANT SELECTIVITY

The ratio of the potencies of a drug on 2 measures yields the "selectivity" of the drug. Any 2 parameters can be compared. For example, the potencies of many tricyclic antidepressants to block NE uptake is comparable to their potencies to block muscarinic cholinergic receptors.[24] Therefore, such TCAs are not selective for these parameters. That is why many of the TCAs will, when given clinically at doses that block NE reuptake, also produce signs and symptoms associated with muscarinic cholinergic blockade, such as blurred vision and dry mouth. Any 2 parameters can be compared for a drug. The advent of the SSRIs, though, produced considerable interest in the selectivity of various antidepressants for blocking 5-HT versus NE uptake. Such values are shown in Figure 3. In this figure, the more selective the drugs are at blocking NE reuptake (vs. 5-HT reuptake), the larger the bar extending to the right. Selectivity of the drugs for 5-HT uptake (vs. NE reuptake) is shown by the magnitude of the bars extending to the left of the figure. It is evident that TCAs such as imipramine and amitriptyline are not very selective, i.e., they are dual-uptake inhibitors, simultaneously blocking the reuptake of both NE and 5-HT.

In general, unless there is about 10-fold selectivity in vitro, there is little likelihood of obtaining selectivity in vivo. Most of the TCAs have considerably greater than 10-fold selectivity for NE, with desipramine in particular

Figure 3. Selectivity of Antidepressants in Blocking NE or 5-HT Reuptake: Ratios of IC_{50} Values for Uptake Inhibition[a]
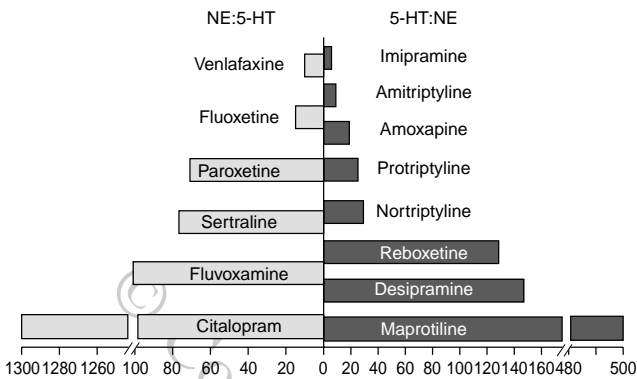
[a]Reprinted, with permission, from Frazer.[4] Abbreviations: 5-HT = serotonin, NE = norepinephrine. To achieve selectivity ratios greater than 1, the IC_{50} value for the monoamine transporter at which the drug is most potent is made the denominator of the ratio.

Table 2. Total Plasma and Cerebrospinal Fluid (CSF) Concentrations of Some Antidepressants

Drug	Protein Binding (%)[a]	Concentration (nM) Plasma	CSF	Reference
Fluoxetine	95	854	26	Martensson et al[30]
(Norfluoxetine)[b]	...	1006	17	
Imipramine	90	433	40	Muscettola et al[31]
(Desipramine)[b]	82–92	431	56	
Imipramine	90	475	36	Hanin et al[32]
(Desipramine)[b]	82–92	642	79	
Nortriptyline	92	443	39	Nordin et al[33]
Paroxetine	95	275	7	Lundmark et al[34]

[a]Protein-binding values from van Harten,[27] Sallee and Pollock,[28] and Benet et al.[29]
[b]Parentheses indicate measurements were taken of the drug as a metabolite of the parent antidepressant.

being a very selective noradrenergic reuptake inhibitor, as are reboxetine and maprotiline. By contrast, citalopram is far and away the most selective of the SSRIs. The original SSRI used clinically, fluoxetine, is not very selective; about 15-fold. However, that degree of selectivity of fluoxetine (and its principal metabolite, norfluoxetine)—given their plasma concentrations—seems sufficient for fluoxetine to maintain selectivity clinically as an inhibitor of 5-HT uptake.[25] Venlafaxine is interesting with respect to its selectivity in vitro and in vivo. Normally, one might not expect its modest selectivity of 5- or 6-fold for blocking 5-HT reuptake to be sufficient to produce selective effects in vivo. Nevertheless, venlafaxine does seem to have a dose-dependent pharmacology. Clinically, at low doses, it seems to be primarily serotonergic; when the dose is raised, noradrenergic effects begin to occur.[26]

ANTIDEPRESSANT CONCENTRATIONS IN CEREBROSPINAL FLUID (CSF)

In considering the likelihood of a drug producing a specific pharmacologic effect in vivo and/or doing so in a "selective" manner, it becomes necessary to know how much drug gets to its site(s) of action. Since antidepressants presumably need to act on brain to exert their beneficial effects, a factor that influences substantially how much drug gets there is the extent to which they are protein bound. Because of the blood-brain barrier, the amount of drug present in the extracellular fluid of brain (e.g., CSF) tends to be equivalent at steady-state to the non–protein-bound drug concentration in plasma (i.e., "free" drug). Normal CSF contains so little protein that it may be regarded as an ultrafiltrate of serum. Since most, but not all, antidepressants are extensively bound to plasma proteins,[27–29] their concentration in CSF is only a small fraction of total drug present in serum.

Table 2 shows values for the percentage of protein binding of certain antidepressants. Also shown are steady-state total plasma concentrations and CSF concentrations of drug. It is apparent that drug measured in CSF approximates what would be calculated to be the "free," i.e., non–protein-bound, concentration in plasma. It is possible, then, to estimate concentrations in CSF for antidepressants for which this has not been reported. Protein binding for citalopram is about 50%[27] and for venlafaxine (or its metabolite O-desmethylvenlafaxine) is about 27% to 30%.[29] Total plasma concentrations of citalopram found clinically range from 40 to 75 nmol/L,[35,36] whereas for venlafaxine (plus O-desmethylvenlafaxine), values are 370 to 3000 nmol/L. On the basis of the percent protein binding for each drug, then, concentrations of citalopram in CSF could range from 20 to 375 nmol/L and those for venlafaxine and its metabolite from 100 to 850 nmol/L.

It is possible, then, to compare CSF concentrations of antidepressants with their K_i values for inhibition of 5-HT or NE reuptake (Table 3). For citalopram, even its lowest concentration in CSF is sufficient to produce essentially complete blockade of 5-HT reuptake. By contrast, even the highest concentration of citalopram in CSF is insufficient to produce appreciable blockade of the noradrenergic transporter. This analysis reveals that, although fluoxetine is less selective than citalopram, the same conclusion is reached. Furthermore, this analysis demonstrates why desipramine and nortriptyline function essentially as selective inhibitors of NE reuptake in brain in vivo. Even though paroxetine has the greatest potency for blocking NE reuptake among the SSRIs, it is not going to cause appreciable blockade of the noradrenergic transporter at these CSF concentrations. There will, though, be essentially complete blockade of 5-HT reuptake. It seems unlikely, then, that paroxetine will produce a degree of inhibition of NE uptake that is functionally significant (i.e., sufficient to enhance noradrenergic transmission) in most patients. There are considerable data in vivo that paroxetine maintains selectivity as an inhibitor of 5-HT reuptake.[26,37,38] Paroxetine does decrease concentrations

Table 3. Cerebrospinal Fluid (CSF) Concentrations of Antidepressants Versus K_i Values Required to Block 5-HT or NE Reuptake[a]

| Drug	CSF (nmol/L)	K_i nmol/L	
		5-HT	NE
Citalopram	20–375	1.4	> 3000
Desipramine	55–80	180	0.6
Fluoxetine	40–50[b]	14	143
Nortriptyline	40	150	2
Paroxetine	7–15	0.7	33
Venlafaxine	100–850	39	210

[a]Potencies of drugs for blocking uptake of [3H]5-HT or [3H]NE into rat brain synaptosomes are from Bolden-Watson and Richelson[17]; these values tend to be in good agreement with those reported by others. Potencies for citalopram are from Hyttel[21] and Hyttel and Larsen.[22] Abbreviations: 5-HT = serotonin, NE = norepinephrine.
[b]Includes norfluoxetine.

Figure 4. Neurotransmitter Depletion Studies[a]

[a]Adapted, with permission, from Delgado et al.[40] Abbreviations: 5-HT = serotonin, NE = norepinephrine, NRI = norepinephrine reuptake inhibitor.

of the NE metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) in CSF of depressed patients,[34] but this effect is produced by many SSRIs, including citalopram,[34,36,39] that are very weak at blocking NE reuptake. It is unlikely, then, that the decrease of MHPG reflects a direct inhibitory effect of paroxetine on the NE transporter.

As suggested in Table 3, venlafaxine (and its metabolite O-desmethylvenlafaxine) is quite likely to inhibit 5-HT uptake, even at the low end of its concentration in CSF. As its concentration in CSF rises, presumably a function of higher doses, venlafaxine begins to reach concentrations capable of blocking NE reuptake. Thus, venlafaxine would not appear to be an SSRI at higher doses. Unfortunately, it is unclear at what doses venlafaxine becomes noradrenergic. Some data suggest that this might occur at 150 mg,[26] but more studies are required. It is generally believed that noradrenergic effects occur at doses of 150 mg or higher.

So, there are antidepressants that are selective in vivo (e.g., desipramine, citalopram), others that are nonselective (e.g., imipramine and amitriptyline), and a drug that has a dose-dependent nonselectivity (venlafaxine). A question, then, is whether pharmacologic selectivity in vivo maintains functional (or therapeutic) selectivity. The studies of Delgado and associates[40] favor the idea of therapeutic selectivity. The results of these studies are indicated schematically in Figure 4. The rationale was to study depressed patients who responded to treatment with either SSRIs or drugs that selectively block the reuptake of NE, e.g., desipramine. Such patients were then given treatments that deplete selectively either 5-HT or NE, and whether depressive symptomatology returned was measured. Depletion of 5-HT in responders to SSRIs caused depressive symptoms to return. By contrast, depletion of 5-HT in responders to drugs that selectively block NE reuptake did not cause the symptoms to return. If NE was depleted in responders to drugs that selectively block NE reuptake, though, symptomatology returned. The simplest interpretation of such data is that the SSRIs are working through a mechanism that does not involve NE and the
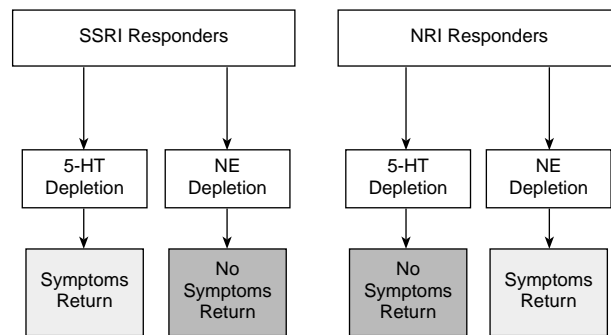
noradrenergic drugs are working through a mechanism that does not involve 5-HT. Thus, it seems that "therapeutic selectivity" accompanies pharmacologic selectivity.

However, noradrenergic and serotonergic neurons interact with each other, either directly or indirectly.[12,41–44] Consistent with earlier immunohistochemical results, my colleagues and I found, for example, a very high density of serotonergic neurons in the noradrenergic cell body area, the locus ceruleus. The binding of the highly selective radioactive ligand [3H]cyanoimipramine to the 5-HT transporter revealed an even higher density of transporter binding sites (indicative of extensive serotonergic innervation) in the locus ceruleus than that found in other terminal fields such as the cortex or amygdala (Figure 5) (A.F., unpublished data, and references 45 and 46). Similarly, the density of noradrenergic transporters in the dorsal raphe nucleus, as revealed by the number of sites labeled by [3H]nisoxetine, a selective ligand for this transporter, is comparable to that found in many other areas of brain (Figure 6) (A.F., unpublished data, and reference 47). Such types of anatomical interactions provide the rationale for the ability of mirtazapine, an α_2-adrenoceptor antagonist, to enhance serotonergic transmission.[24]

Such anatomical interactions, coupled with physiologic effects, might underlie the ability of selective reuptake inhibitors to produce apparently nonselective effects in patients. For example, essentially all SSRIs decrease not only the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) in CSF of patients treated with these drugs but the NE metabolite MHPG as well.[39] On the other hand, drugs that selectively block NE reuptake decrease 5-HIAA as well as MHPG.[39] In general, SSRIs seem to have less of an effect on MHPG than on 5-HIAA, and the reverse is true for drugs that selectively block NE reuptake. However, the data of Delgado and associates[40] might indicate that these nonselective pharmacologic effects do not have therapeutic significance. What seems safest to conclude is that reuptake inhibitors enhance serotonergic and/or nor-

Figure 5. Binding of [³H]Cyanoimipramine ([³H]CN-IMI) to the Serotonin Transporter in Regions of Rat Brain[a]
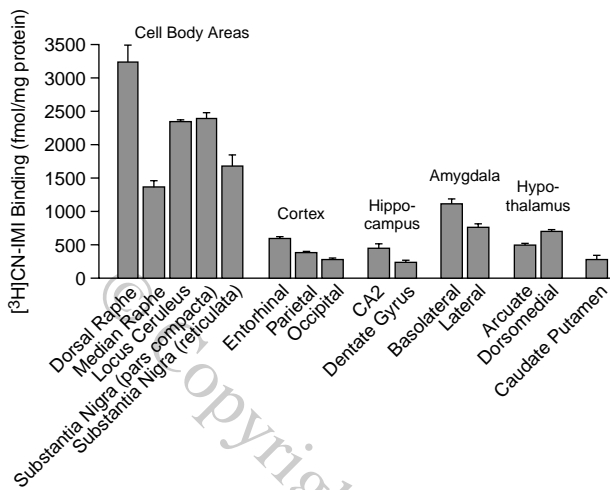
[a]A.F., unpublished data; binding of the radioligand and quantitative analyses of the autoradiograms were carried out as described by Kovachich et al.[45] and Hensler et al.[46] High binding is present in both noradrenergic and dopaminergic cell body areas.

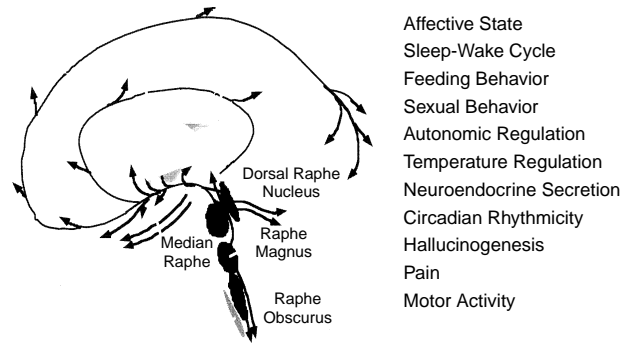Figure 6. Binding of [³H]Nisoxetine to the Norepinephrine Transporter in Regions of Rat Brain[a]
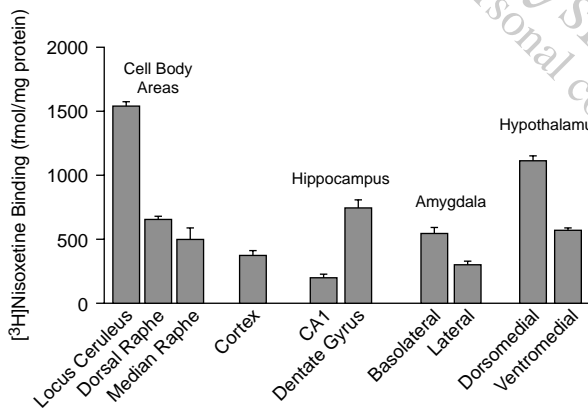
[a]Data from Tejani-Butt[47] and A.F., unpublished data. In general, binding in serotonergic soma such as the dorsal and median raphe nuclei is as high as that seen in many terminal fields.

adrenergic transmission. The question, then, is how such pharmacologic effects induce therapeutic improvement in depression and anxiety disorders.

BEHAVIORAL ROLES FOR 5-HT AND NE

Of course, the answer to this is not known. Both 5-HT and NE have been implicated in many behaviors. Some of the behaviors in which 5-HT is involved are shown in Figure 7, and those for NE in Figure 8. One issue worth considering is that these biogenic amines do not seem to be the key transmitters that drive these behaviors in, for

Figure 7. The Serotonin System[a]

Affective State
Sleep-Wake Cycle
Feeding Behavior
Sexual Behavior
Autonomic Regulation
Temperature Regulation
Neuroendocrine Secretion
Circadian Rhythmicity
Hallucinogenesis
Pain
Motor Activity

[a]Schematic of the serotonergic innervation of brain and some of the behaviors thought to be regulated by serotonin.

Figure 8. The Norepinephrine System[a]
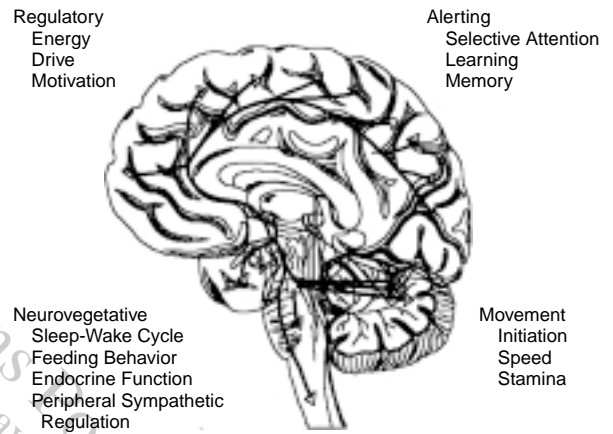
[a]Schematic of the noradrenergic innervation of brain and some of the behaviors thought to be regulated by norepinephrine.

example, the way dopamine drives extrapyramidal loco-motor activity. Rats with lesions of dopamine neurons have locomotor defects. By contrast, the behavioral de-fects seen in animals with lesions of noradrenergic or serotonergic neurons are more subtle, suggesting perhaps that these amines modulate or regulate many behaviors, but do not mediate them. If one accepts this view, it might be useful to consider more global behaviors influenced by 5-HT or NE such that effects on these global behaviors, or behavioral states, could affect more specific behaviors such as feeding or learning and memory.

For 5-HT, a case has been made that it is involved in behavioral inhibition or in constraining behavioral activa-tion, particularly in situations involving a degree of com-petition between behavioral suppression and active re-sponding.[48–50] This view would posit that inhibition, passivity, and waiting are the main neuropsychological concomitants of the control of behavior by 5-HT. Thus, decreased 5-HT transmission would lower the threshold

Alan Frazer

for passivity or constraint tolerance. The specific association claimed for low 5-HT level with aggression[50] would fit well into this larger behavioral framework.

On the other hand, there are considerable data showing changes in 5-HT release in specific terminal fields in response to specific stimuli.[50] This might indicate that, although it may be heuristically useful, the involvement of 5-HT in behavior is quite likely to be more complex than can be accounted for by theories suggesting it has some uniform general behavioral role. The situation becomes even more complex in light of the multiplicity of receptors for 5-HT.[51] An example of such complexity is shown in the behavioral phenotypes of mice genetically engineered to lack certain receptors for 5-HT. In mice lacking the 5-HT$_{1A}$ receptor (5-HT$_{1A}$ knockout mice), behavioral measures thought to reflect anxiety are increased, and those reflective of aggression are decreased.[52] The exact opposite behavioral effects are seen in mice lacking the 5-HT$_{1B}$ receptor.[52] Since 5-HT reuptake inhibitors are presumably enhancing serotonergic transmission at all 5-HT receptors, it becomes highly speculative how nonspecific enhancement of serotonergic function produces anxiolytic or antidepressant effects.

As shown in Figure 8, NE is also involved in many different behaviors. Perhaps the strongest case for a behavioral role for NE can be made for its involvement in behavioral arousal (or alerting or vigilance[53]). Only stimuli considered of significance to the organism activate the locus ceruleus so as to enhance attentional and emotional processes. Involvement of NE in such processes results, perhaps, in drug-induced activation of central noradrenergic pathways being helpful in overcoming the limited emotionality, flat affect, and, perhaps, even anhedonia that are associated with depression. Which of the many noradrenergic receptor subtypes that may be involved in such behavioral effects are involved is unknown. Other behaviors in which NE has been implicated, either specifically or because of its role in behavioral arousal, include learning (or subprocesses that contribute to it, such as attention) and cognition, the cycling of sleep and wakefulness, and perhaps feeding behavior. Again, these behaviors are known to be altered in patients with depression. It may well be that the activation of central noradrenergic neurons is useful in restoring normal behavioral functioning. It is conceptually more challenging to think of how such behavioral effects of NE produce amelioration of anxiety symptoms, especially given the known activation of central noradrenergic neurons in response to stressors.

In summary, then, a necessary but perhaps not a sufficient effect that underlies the therapeutic efficacy of 5-HT and/or NE reuptake inhibitors in depression as well as in several anxiety disorders is enhancement of serotonergic and/or noradrenergic transmission. Much more research will be needed, though, to clarify how such neurochemical actions produce behavioral effects.

Drug names: amitriptyline (Elavil and others), bupropion (Wellbutrin), citalopram (Celexa), desipramine (Norpramin and others), doxepin (Sinequan and others), fluoxetine (Prozac), fluvoxamine (Luvox), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Pamelor and others), paroxetine (Paxil), phenelzine (Nardil), protriptyline (Vivactil), sertraline (Zoloft), tranylcypromine (Parnate), trimipramine (Surmontil), venlafaxine (Effexor).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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