Monoaminergic systems have long been implicated in the pathophysiology and/or the therapeutics of mood disorders. These are old systems on the phylogenetic scale, which has allowed their in-depth studies in the rodent brain with the results being extrapolated to humans with striking consistency. Mother Nature has built-in mechanisms in these systems to maintain their homeostasis. Indeed, they exert such important roles in the brain within the animal kingdom, including non-human primates and humans, and the maintenance of their normal function plays a crucial role in survival. The level of redundancy appears to be of the order of 80%, meaning that alterations of various parameters controlling the function of these systems has to reach an approximate threshold of 80% change before a net change in transmission can occur. This is highly relevant to human therapeutics because it implies that there should not be a linear relationship between interference with a monoaminergic neuronal element, such as reuptake transporter, and a clinical phenomenon. Some examples are given here.

In Parkinson’s disease, patients begin to show motor symptoms when there is an approximate loss of 80% of dopamine neurons in the substantia nigra (Agid, et al., 1987). These neurons give rise to the dopaminergic innervation of the striatum, which plays a crucial role in motor function. Consistent with the above-mentioned figure, 80% of striatal dopamine type 2 receptors need to be blocked by antipsychotic medications to lead to extrapyramidal symptoms. In Alzheimer’s disease, approximately 75% of the cholinergic neurons in the basal forebrain are lost when symptoms (Farde et al., 1992) appear (McGeer, et al., 1984). These neurons provide the cholinergic innervation to the cerebral cortex. Acetylcholine is generally not thought of as a monoamine, such as serotonin (5-HT), noradrenaline (NE) or dopamine, but it has a single quaternary amine (a positively charged nitrogen atom with three methyl groups). Approximately, 70-80% of monoamine oxidase (MAO) need to be inhibited before an antidepressant action can occur with inhibitors of this enzyme (Zimmer, 1990). This was determined from MAO-B inhibition and the decrease of 3,4-dihydroxyphenyl-ethyleneglycol in the blood to assess MAO-A inhibition. Finally, the minimal effective doses of the serotonin reuptake inhibitors (SRIs) produce an 80% occupancy of 5-HT transporters (5-HTTs) in the human brain, as measured by positron emission tomography (PET; Meyer, et al., 2004).

Experimental results in the rodent brain are consistent with the above observations. In the NE system, approximately 90% of NE neurons need to be lesioned before attenuating the effect of the stimulation of the NE pathway on postsynaptic neuron firing in the hippocampus (Curet and de Montigny, 1988). In the 5-HT system, an approximate 80% decrease in tissue 5-HT content leaves extracellular 5-HT levels unaltered in the rat striatum (Kirby, et al., 1995). In the dopamine system, extracellular levels are maintained until 80% of control tissue content is eliminated (Castañeda, et al., 1990).

Why is this relevant to current drug development? Because selective 5-HT, NE or dopamine agents can produce an antidepressant action on their own, it is generally accepted that the combination of at least two effects can produce a greater therapeutic effect. This is supported by the effectiveness of augmentation or combination strategies in patients not responding to a selective agent (Blier, 2006). In the case of the dual 5-HT/NE reuptake inhibitors, venlafaxine and duloxetine, biochemical data are consistent in showing their potent action on the 5-HT transporter (Turcotte, et al., 2001; Vincent, et al., 2004; Blier, et al., 2007). With concentration or dose increments, the NE transporters (NETs) are progressively inhibited. Regarding NET inhibition, the main issue is at what dose(s) or concentration(s) are NETs inhibited to an extent that significantly impacts overall NE transmission? In the case of venlafaxine, 75 mg/day produces the above mentioned 80% occupancy of the 5-HTT, which corresponds to its minimal effective dose in depression (Meyer, et al., 2004). Similarly, the minimal
effective dose of duloxetine in major depression (60 mg/day) also produces a sustained 80% occupancy of the 5-HTT (Takano, et al., 2006). Unfortunately, an established PET ligand for the NET is not yet available.

Two main approaches have been used in humans to study the NET. The first consists in taking the plasma of patients treated with reuptake inhibitors and incubating it with a cell line expressing the human NET and 5-HTT. With this *ex vivo* method, the minimal effective doses of the SRI paroxetine and venlafaxine produce an approximate 60% inhibition of the 5-HTT (Owens, et al., 2008). This approach, therefore, appears to underestimate the occupancy of the 5-HTT in the brain by approximately 20%. Such a direct comparison for the NET cannot be made because of the lack of a PET ligand. Nevertheless, 225 mg/day of venlafaxine, a regimen generally considered a NE dose, produces a 50% inhibition of the NET *ex vivo*, whereas paroxetine 50 mg/day results in approximately 30% inhibition (Owens, et al., 2008). The other approach consists in injecting intravenously tyramine, which penetrates peripheral NE terminals through NETs and release NE, which in turn triggers a dose-dependent increase in systolic blood pressure. Blockade of NET attenuates the transient systolic blood pressure increase. In this model, tricyclic antidepressants, reboxetine and atomoxetine attenuate the pressor response, whereas paroxetine (20–50 mg/day) and sertraline (50 mg/day) are inactive (Blier, et al., 2007). Venlafaxine exerts a significant action at 225 mg/day or more (Debonnel, et al., 2007). Consequently, if the *ex-vivo* method underestimates NET occupancy by 20% as is the case with for the brain 5-HTT, the clinically relevant level of NET inhibition in the brain by 225 mg/day of venlafaxine would be around 70%, a value not far from the above mentioned standard 80% figure.

Given that triple reuptake inhibitors are currently in development, this occupancy issue is also crucial to the dopamine reuptake transporter (DAT): what is the degree of DAT occupancy that is necessary before significantly altering dopamine transmission? Although DAT occupancy can be assessed in the human brain with PET, there is no established antidepressant with physiologically significant dopaminergic activity. In conclusion, it will be interesting to follow the development of a PET ligand for the NET and of dopamine reuptake inhibitors in the treatment of depression to see whether the 80% threshold that applies to the 5-HT system will also be relevant to the NE and dopamine systems.

**References**


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