Site Specific Drug Action

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Abstract

A model to facilitate site specific action of a given drug is offered. The model is controlled by the internal biochemistry of the organism. If site specificity can be achieved, side effects would be greatly diminished. An example of chlorpromazine and dopamine is described.

The side effects of psychotropic drugs involves some degree of lack of specificity for their site of action. For example, a major side effect of chlorpromazine, tardive dyskinesia, is induced by unwanted drug action in 'motor' regions. It would be advantageous if a drug such as chlorpromazine could come in contact only with those neural regions linked with psychotic functioning. Systemic administration makes this specificity impossible.

In this paper I offer a theoretical way of facilitating anti-psychotic drug specificity. The model relies upon the brain's internal biochemistry more than it relies upon the drug. The proposal will provide pharmacologists, nutritionists and those involved in the study of psychotic functioning with a new way of considering drug action.

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Emotional and motor regions seem separated in the brain. It is certainly not unreasonable to assume that there are biochemical differences, as well as morphological ones, from one brain region to another. The biochemical differences we will be concerned with are varying concentrations and types of neurotransmitter degrading enzymes.

If we can locate different kinds of degrading enzymes, or even varying concentrations of the same one, in different brain regions, preferential longevity of a drug can be mediated. In other words, if there is more of an enzyme in a given tissue which will degrade a certain substrate, less of that substrate will remain in that tissue compared to another tissue lacking the degrading enzyme. From this notion, virtual elimination of side effects is possible.

Perhaps it is found in the 'emotional' region that there exists an abundance of the degrading enzyme A which selectively cleaves substrate A'. In the 'motor' regions there is similarly enzyme B which cuts B'.

Next, we connect the substrates A' and B' via a "bridge". Adjacent to the points of attachment of the two substrates A' and B' we add on, for example sake, chlorpromazine

and dopamine respectively. Our resulting structure will look like:

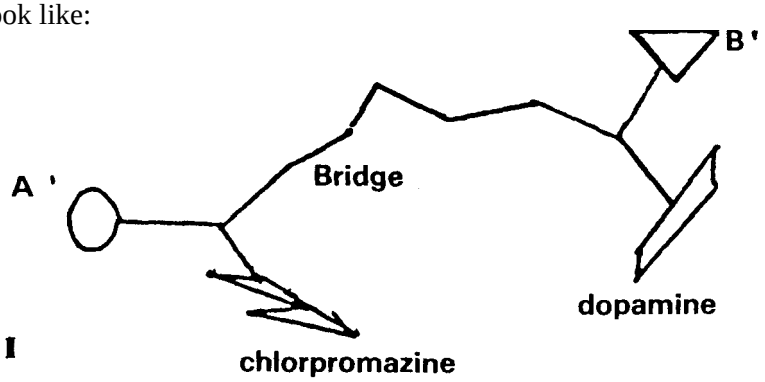

Figure I

Upon entry into the whole brain, our new complex compound should be relatively evenly distributed. In the region where there exists an abundance of degrading enzyme A, however, the large molecule will be cut at A'. This should, if the new compound is constructed correctly, free the chlorpromazine from the bridge. The liberation of chlorpromazine would occur due to destabiliza-tion of the whole parent compound. The result: the chlorpromazine will be liberated, free to act in the appropriate brain region while the dopamine still has the bridge, as well as B' attached to it. It would remain inert.

Similarly, in the 'motor' region where there is an abundance of enzyme B, the dopamine would be liberated. In this instance, the chlorpromazine would be inactive as the "bridge" remains attached.

Thus far, the assumption has been made that there are different degrading enzymes. This need not be the case: only differing concentrations of the same enzyme are required to selectively favor freedom of the functional drug. One site would be cleaved with greater probability than the other.

To put this model to work we must: 1) identify different degrading enzymes or different concentrations of the same one, and, 2) a suitable new structure must be created that is stable, has no intrinsic side effects or toxicity, can enter the brain and function as per the previous discussion.

Even with all of the "suppose-ifs", this model, should it be made functional, would eliminate many ineffective poly-drug techniques and allow us to construct drugs which lack side effects due to non-specific site of action. Clearly, though a long-shot, such a proposal is worthy of investigation by virtue of its implications. Even if not useful in the case of psychotropic drugs, such a framework may provide therapies in systems where the biochemistry has been well established.