Liquid membrane phenomena in the multiple actions of psychotropic drugs†

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Multiplicity of biological actions of surface active psychotropic drugs has been discussed in the light of modifications in the permeability of relevant neurotransmitter molecules viz. dopamine, noradrenaline, adrenaline, γ-aminobutyric acid (GABA) and serotonin through the liquid membranes generated by these drugs. It has been shown that modification in the transport of relevant permeants through the drug liquid membranes likely to be generated at various sites of action may provide a generalized explanation for multiple actions of the surface active drugs. The drugs chosen for the present discussion are, haloperidol, chlorpromazine, reserpine and imipramine. The data published earlier on the transport of relevant permeants through the liquid membranes generated by these drugs have been utilised for the present discussion.

Introduction
Recent studies on a wide variety of surface active drugs belonging to different pharmacological categories have led to what may be termed as liquid membrane hypothesis for drug action. The central idea of the hypothesis is that the liquid membranes generated by the drugs at the respective sites of action, modifying the transport of relevant permeants to these sites, may be an important step, common to the mechanism of action of all surface active drugs. It has been shown that this concept when viewed in the light of existing theories of drug action, particularly the occupancy theory and the rate theory, yields a more rational biophysical explanation for the action of such drugs which act by modifying the permeability of cell membranes. A concise account of the liquid membrane hypothesis for drug action, which has been substantiated in a good number of cases, and its implications have been presented in the review article by Srivastava, Bhise and Mathur. One important implication of the liquid membrane hypothesis for drug action is that it can offer a generalised explanation for the multiplicity of biological actions exerted by surface active drugs. It has been argued that the multiplicity of biological actions exerted by surface active drugs can be explained on the basis of alteration in the transport of relevant permeants because of the drug liquid membrane interposed between the permeant and the site of action.

Discussion
The normalised values of solute permeability for relevant permeants in the presence of the drug liquid membranes in case of each of the four psychotropic drugs viz. haloperidol, chlorpromazine, reserpine and imipramine as obtained in the earlier studies are recorded in Table 1. The data in Table 1 are from two sets of model experiments, the one in which the permeants face hydrophilic surface of the drug liquid membrane and the other in which they face the hydrophobic surface. For experimental details the original papers should be referred to.

Clinically chlorpromazine, haloperidol and reserpine are used as antipsychotics whereas imipramine is used as an antidepressant. In addition to antipsychotic and antidepressant effects, these drugs are reported to exert a variety of other biological actions as well (multiplicity of drug action). In what follows we present a rationale for the multiple biological actions of these drugs in terms of liquid membrane hypothesis for drug action.

It is well known that central regulation of the pituitary is mediated by the hypothalamus which in turn is under the influence of neurotransmitters. It is.
away from it. Therefore the agonist, dopamine, phobic parts of the drugs would be drawn outwards and neurohypophysin.

Dopamine, nor-adrenaline and adrenaline which are known to be dopamine antagonists, the hydrophilic parts of the drugs would be preferentially oriented towards the hydrophilic parts of the receptor and the hydrophobic parts of the drugs would be drawn outwards away from it. Therefore the agonist, dopamine, molecules would face the hydrophobic surface of the drug liquid membranes interposed between the agonist and its site of action. Thus the data (Table 1) on the transport of dopamine in the specific orientation of the drug liquid membranes with its hydrophobic surface facing the permeant, dopamine, appear relevant to its biological actions. Similar considerations apply to adrenaline and nor-adrenaline and also to serotonin, which act on pre- and postsynaptic receptors.

Neurotransmitters through their action on median eminence promote or inhibit the release of hypophysiotrophic hormones, both release and release inhibiting hormones. These hypophysiotropic hormones in turn act on adenohypophysis and regulate the release of adenohypophysins.

Dopamine, nor-adrenaline and adrenaline are reported to inhibit the release of CRH (corticotropin releasing hormone). This inhibition of the release of CRH in turn inhibits the release of ACTH (adrenocortico tropic hormone). The neuroleptic drugs namely haloperidol, chlorpromazine and reserpine which impede the transport of dopamine, nor-adrenaline and adrenaline (Table 1) and thereby reduce the access of these neurotransmitters to their site of action in median eminence should enhance the release of CRH and consequently of ACTH. This expectation is in agreement with literature reports that administration of these drugs viz. haloperidol, chlorpromazine and reserpine does enhance the release of ACTH. The role of serotonin, whose permeability is reduced in the presence of imipramine (Table 1), on the release of ACTH is complicated. Both stimulatory and inhibitory actions have been reported. This is consistent with the fact that no significant effect of imipramine, which blocks both pre- and postsynaptic receptors, on the release of adenohypophysins including ACTH have been reported. Gamma aminobutyric acid (GABA) is known to have inhibitory effect on the release of CRH. The impediment in the transport of GABA in the presence of the three neuroleptics haloperidol, chlorpromazine and reserpine (Table 1) in the specific orientation of the drug liquid membranes with their hydrophobic surface facing the permeants is consistent with the reported enhancement in the release of ACTH by these drugs.

It is documented that dopamine, and GABA have inhibitory effects on the release of TSH (thyroid stimulating hormone) whereas nor-adrenaline and adrenaline have stimulatory effects. The impediment in the transport of nor-adrenaline and adrenaline in the presence of the chlorpromazine liquid membrane (Table 2) could be a plausible expla-

<table>
<thead>
<tr>
<th>Permeants</th>
<th>Permeant facing the hydrophobic surface of the drug liquid membrane</th>
<th>Permeant facing the hydrophilic surface of the drug liquid membrane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>$r_1$ = 0.766</td>
<td>$r_2$ = 2.938</td>
</tr>
<tr>
<td>Chlorpromazine hydrochloride</td>
<td>$r_1$ = 0.340</td>
<td>$r_2$ = 0.524</td>
</tr>
<tr>
<td>Imipramine hydrochloride</td>
<td>$r_1$ = 0.539</td>
<td>$r_2$ = 0.777</td>
</tr>
</tbody>
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Table 1—Normalized values ($r$) of solute permeability in the presence of liquid membranes generated by the drug: $r = \frac{w}{w_{control}}$, $w$ being the value of solute permeability given by the equation $w = \frac{J}{A\Delta x}$, $J$, and $J$, represents the solute flux and the volume flux per unit area of the membrane and $A\Delta x$ is the osmotic pressure difference across the membrane and $w_{control}$ being the value from control experiments in which no drug was used.

$r_1$: permeants facing the hydrophobic surface of the drug liquid membrane.

$r_2$: permeants facing the hydrophilic surface of the drug liquid membrane.

The permeants are categorized into three groups:

1. **Dopamine**
2. **Nor-adrenaline**
3. **Adrenaline**
4. **Serotonin**
5. **GABA (gamma aminobutyric acid)**

For the actions of dopamine the hydrophilic portions of dopamine receptors which are located in higher brain centres have been considered to be important. It is therefore expected that in the liquid membranes formed at the site of action by haloperidol, chlorpromazine or reserpine which are known to be dopamine antagonists, the hydrophilic parts of the drugs would be preferentially oriented towards the hydrophilic parts of the receptor and the hydrophobic parts of the drugs would be drawn outwards away from it. Therefore the agonist, dopamine,
nation for the reported inhibition of TSH release by chlorpromazine. It has been reported, that chlor-
pronazine has specific affinity for accumulation in the hypothalamic area.

At hypothalamic level, the secretion of prolactin in mammals is controlled by the inhibitory hormone P-RIH (prolactin release inhibiting hormone) and possibly a prolactin releasing hormone, P-RH, the role if any of P-RH is only of secondary importance. The release of P-RH from the hypothalamus is controlled primarily by hypothalamic dopamine. Neuroleptic drugs which inhibit the transport of dopamine (Table 1) are therefore expected to enhance the prolactin secretion which indeed is substantiated by literature reports. It may be mentioned that there are very strong evidences to suggest that dopamine itself functions as P-RIH.

The role of GABA in the secretion of prolactin is similar to that of dopamine at the level of median eminence and also at the hypophyseal level. The impediment in the transport of GABA due to the liquid membranes generated by the neuroleptic drugs (Table 1) could also be a factor contributing to the increased prolactin secretion brought about by the neuroleptics. The role of adrenaline, nor-adrenaline and serotonin at the level of median eminence, in prolactin secretion is stimulatory in nature, the magnitude of the stimulatory effect being much smaller in comparison to the inhibitory effect of dopamine.

The neuroleptic drugs which inhibit the transport of dopamine (Table 1) should therefore, bring about a decrease in prolactin release on account of impediment in the transport of serotonin, nor-adrenaline and adrenaline due to the liquid membranes generated by these drugs. In order that this effect becomes observable, one should first block the dopamine receptors and then study the effect of neuroleptics on prolactin release. Such experiments which are carried out to substantiate this surmise have however not come to our notice.

At the hypophyseal level the effects of nor-adrenaline and adrenaline on the release of prolactin are similar to that of dopamine. It has been shown that adding extracts of hypothalamus to the cultured anterior pituitories decreased the quantity of prolactin released into the medium. Danon et al. showed that hypothalamus obtained from rats treated with a phenothiazine derivative, perphenazine, when added to the cultures of pituitaries does not inhibit prolactin secretion. The impediment in the transport of nor-adrenaline, adrenaline and dopamine due to the liquid membranes of phenothiazine drugs like chlorpromazine (Table 1) could be a plausible explanation for the antagonistic effect of phenothiazine on the normally operating inhibitory influence of the hypothalamus on prolactin secretion at the level of pituitary.

The fact that dopamine plays a key role at the level of median eminence in stimulating the release of LH/FSH-RH (luteinizing hormone/follicle stimulating hormone-releasing hormone) is well established. The release of dopamine at the median eminence is in turn controlled by other neurotransmitters viz. nor-adrenaline, adrenaline, GABA, serotonin and also dopamine at the higher brain centres. The observation that neuroleptics like chlorpromazine, haloperidol and reserpine block the release of LH/FSH-RH can be explained in terms of the resistance offered to the transport of the neurotransmitters by the neuroleptic drugs (Table 1) which are known to accumulate not only in the median eminence but also in the higher brain centres.

Dopamine and nor-adrenaline have been reported to increase growth hormone release in animals and man. Neuroleptic drugs like haloperidol, reserpine, chlorpromazine etc. caused reduction in the release of growth hormone. The impediment in the transport of these neurotransmitters viz. dopamine and nor-adrenaline (Table 1) due to the liquid membranes generated by the neuroleptic drugs can be utilized to explain this observation—the liquid membranes reduce the access of the neurotransmitter to their action sites.

Dopamine which acts not only on the median eminence but also on somatotrophs has a paradoxical inhibitory effect on the release of growth hormone in acromegalis. This is attributed to somatotrophic cells themselves. It may be mentioned that treating acromegaly with phenothiazines which inhibit the transport of dopamine (Table 1) has met with little success. This is not unexpected in view of the paradoxical inhibitory action of dopamine in the release of growth hormone in acromegalic patients.

MSHs (melanocyte stimulating hormones) secretion by the pars intermedia of pituitary gland is inhibited by catecholamines viz. nor-adrenaline, adrenaline and dopamine. Neuroleptic drugs such as haloperidol, reserpine and chlorpromazine are reported to stimulate MSH secretion. This is an expected observation in view of the reduced permeability of adrenaline, nor-adrenaline and dopamine in the presence of the liquid membranes generated by the neuroleptic drugs reducing access of the catecholamines to their relevant sites of action.

Neurohypophysial secretions containing ADH (antidiuretic hormone), oxytocin and neurophysins are evoked by different stimuli. Acetylcholine and nicotine injected into carotid circulation cause the release of ADH, oxytocin and neurophysins while
nor-adrenaline inhibits their release. It is therefore logical to expect that the drugs like chlorpromazine and reserpine which are likely to reduce the access of nor-adrenaline to the relevant site of action due to its reduced permeability through the liquid membranes generated by these drugs (Table 1) should reduce the inhibitory effect and thereby facilitate the release of neurohypophysial hormones like ADH, oxytocin etc. This indeed has been found to be the case.

Reduction in the concentration of serotonin at the post synaptic receptor resulting in defective neurotransmission has been implicated in migraine. Imipramine in some cases is known to act beneficially in migraine, whereas neuroleptics like reserpine are known to aggravate it. Blockade of reuptake of serotonin due to its reduced permeability through the imipramine liquid membrane (Table 1) likely to be formed at the presynaptic receptors resulting in improved neurotransmission could also be a possible explanation for the curative action of imipramine. Similarly blockade of serotonin due to its reduced permeability through the liquid membranes likely to be generated by the neuroleptic drugs (Table 1) at the post synaptic receptor resulting in poor neurotransmission could be a plausible explanation for the aggravation of migraine by the neuroleptic drugs like reserpine.

Neuroleptic drugs e.g. haloperidol, chlorpromazine, and antidepressant drugs like imipramine are reported to cause hypothermia. This effect can also be explained on the basis of the modification in the permeability of neurotransmitters due to the liquid membranes which may be formed by these drugs in the hypothalamic region. The hormones ACTH/MSH whose secretion is inhibited by nor-adrenaline, adrenaline and dopamine at the level of median eminence have been shown to cause a fall in body temperature. Since the neuroleptic drugs and also the antidepressant drugs like imipramine reduce the permeability of nor-adrenaline, adrenaline and dopamine (Table 1), the presence of these drugs at the hypothalamic level may reduce the access of these neurotransmitters to the relevant sites of action causing thereby an increase in the secretion of ACTH/MSH. This in turn may be responsible for the hypothermic effect. The poikiloerthermic effect of chlorpromazine which is sometimes used to facilitate the induction of surgical hypothermia can also be rationalised in terms of modification in the permeability of neurotransmitters due to the presence of neuroleptic drugs like chlorpromazine (Table 1). Neurotransmitters have also been implicated in central regulation of body temperature in normothermia. While most neurons are temperature insensitive, warm sensitive neurons and cold sensitive neurons located in the preoptic area and in the anterior hypothalamic area have been implicated in thermoregulation in mammals. The firing rates of warm sensitive neurons increase with warming or decrease with cooling while reverse is the case in cold sensitive neurons. In mammals intracerebroventricular injection of serotonin produces a rise in body temperature. It is therefore logical to guess that serotonin acts on cold sensitive neurons and nor-adrenaline on warm sensitive neurons. It is documented that cold sensitive neurons loose their thermosensitivity during synaptic blockade while the warm sensitive neurons do not. Chlorpromazine during synaptic blockade would therefore impair the thermosensitivity of cold sensitive neurons and leave the thermosensitivity of warm sensitive neurons unaffected leading to poikilothermia.

Parkinson's disease is known to be due to deficiency of neurotransmitters like dopamine in basal ganglia. Neuroleptic drugs e.g. haloperidol, chlorpromazine and reserpine are known to cause Parkinson's disease. Reduced permeability of dopamine (Table 1) in the presence of the liquid membranes likely to be generated by these drugs in the region of basal ganglia could be one of the contributing factors for this side effect i.e. drugs induced Parkinsonism. The extrapyramidal effects of antipsychotic drugs like haloperidol are reported to be resistant to levodopa therapy. Since reduced concentration of serotonin in cerebrospinal fluid has also been linked with a defect of extra-pyramidal function, the reduced permeability of serotonin in the presence of antipsychotic drugs like haloperidol (Table 1) offers a clue to the causation of extrapyramidal symptoms.

Most neuroleptic drugs have marked protective action against nausea and emesis inducing effects of dopamine agonists which can interact with the central dopaminergic receptors in the chemoreceptor trigger zone of the medulla. This effect can also be explained by the reduction in the permeability of dopamine due to the liquid membranes generated by the neuroleptic drugs (Tables 1). It is reported that neuroleptics and also tricyclic antidepressants e.g. imipramine cause orthostatic hypotension. For example, in normal man intravenous administration of chlorpromazine causes orthostatic hypotension due to a combination of central action and peripheral α-adrenergic blockade. Although the actions of these drugs on cardiovascular system are complex because these drugs produce direct effects on the heart and blood vessels and also indirect ones through actions on central nervous system and auto-
onomic reflexes, reduced permeability of noradrenaline in the presence of these drugs (Table 1) could also contribute to the causation of orthostatic hypotension.

Neuroleptic drugs particularly chlorpromazine and reserpine, during coitus, are known to impair ejaculation without interfering with erection\textsuperscript{33,39}. Attribution of this effect to adrenergic blockade though logical remains unsubstantiated\textsuperscript{33}. Reduction in the permeability of noradrenaline due to the liquid membranes generated by the neuroleptic drugs (Table 1) is consistent with the conjecture that impairment of ejaculation may be due to adrenergic blockade.

Conclusion
Thus it appears that modification in the permeability of relevant neurotransmitters due to the liquid membranes generated by the psychotropic drugs may be one of the casual factors for the multiple actions of these drugs.

Acknowledgement
Thanks are due to the UGC, New Delhi for support. We express our gratitude to Mr P Raghunandan of Juggat Pharma, Bangalore (India) and Mr A D Tarnahalli of College of Pharmacy, Belgaum (India) for their help.

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