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THE SURFACE ACTIVITY OF TRANQUILIZERS

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Abstract—1. The potent neuroleptic drugs reserpine, butyrylperazine, fluphenazine, prochlorperazine, trifluperazine, carphenazine, triflupromazine, thioridazine, ethopropazine, and chlorpromazine all lower the surface tension of a Ringer solution, pH 7, at concentrations between 10^{-7} M and 5×10^{-6} M in the given order.

2. Non-neuroleptics imipramine, trimeprazine, promazine, chlordiazepoxide, promethazine, and toluidine blue lower the surface tension at higher concentrations, ranging from 2×10^{-5} M to 5×10^{-4} M. Chlorpromazine sulfoxide barely lowers surface tension at 10^{-3} M.

3. The surface activities of the neuroleptic drugs correlate with the clinical potencies—a 100-fold increase in surface activity is associated with a 100-fold decrease in the average micromolar daily oral dose for clinical acute schizophrenia (predominantly of the paranoid type).

4. The surface tension of schizophrenic plasma is normal and does not change when phenothiazine is added. Urine tension falls upon addition of phenothiazine.

5. The surface tension is lowered by the formation of a virtually monomolecular film at the interface, as shown by compression studies (1 molecule per 87 Å^2). Such an adsorbed film would explain the rapid erythrocyte adsorption of these compounds (about 1 molecule/185 Å^2). It would also explain the generalized reduction in membrane permeability to solutes by virtue of its increasing the effective membrane thickness by a loosely packed "tranquilizing" film 18 Ångstroms thick.

THE MODE of action of the antipsychotic tranquilizers remains unclear. It is known that the phenothiazines inhibit certain enzymes but also reduce membrane permeability. For example, chlorpromazine inhibits mitochondrial respiration and uncouples oxidative phosphorylation[1–4]. However, the concentration of chlorpromazine required for these inhibitions is greater than 1×10^{-4} M to 2×10^{-4} M, at least 50- or 100-fold greater than the plasma concentrations *in vivo* achieved during the tranquilization of the animal or the human being.

The reduction of membrane permeability, on the other hand, usually occurs at more dilute concentrations. The spontaneous swelling of mitochondria of rat liver in isotonic sucrose is inhibited by chlorpromazine, 5×10^{-6} M to 10^{-4} M.[5] Other effects of phenothiazines that have been attributed to changes in membrane permeability have been the inhibition of water uptake by frog muscle[6, 7], the inhibition of erythrocyte hemolysis,[8–11] the inhibition of acetylcholine release,[12] the inhibition of serotonin and noradrenaline uptake in various tissues,[13–17] and finally the inhibition of glycine uptake by brain slices.[18]

In order to separate effects on enzymes from effects on membrane permeability we

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started to study the action of various phenothiazines and other drugs on monolayers of stearic acid and sciatic nerve lipid extracts. During the course of these investigations it was observed that all tranquilizers lower the surface tension of a Ringer solution in close correlation with their clinical antipsychotic potency, regardless of whether they are phenothiazines or not. These surface tension observations are here reported along with some observations on the surface tension of schizophrenic plasma.

Since Traube's pioneering observation[19] that there was a correlation between anesthetic activity and surface activity in the alcohol series, considerable data have accumulated on the surface properties of alcohols, local anesthetics, and various other general anesthetics and hypnotics[20-25]. In the past decade this information on anesthetics has been reviewed and discussed by Butler[26] and also by Pittinger and Keasling.[27] However, the only reported work that seems to be available on the surface activity of phenothiazines is that of Vilallonga *et al.*[28] They studied promazine, promethazine, diethazine, and imipramine at the air–0·1 M HCl interface and observed that the surface tension fell at extremely high concentrations of the order of 5×10^{-2} M and up. In our present study, instead of using a solution with extremely low pH, we have used a Ringer solution buffered at pH 7. None of the compounds studied by Vilallonga *et al.* is "antipsychotic" or "neuroleptic," as defined by Deniker[29] for clinical schizophrenia. In this paper the primary attention has been on these antipsychotic neuroleptic compounds: reserpine, chlorpromazine, butyrylperazine, ethopropazine, fluphenazine, propiomazine, prochlorperazine, thioridazine, trifluperazine, triflupromazine, and carphenazine. For purposes of comparison the mild ataraxics or mild tranquilizers such as chlordiazepoxide and promazine have also been included.

MATERIALS* AND METHODS

Surface tension was measured by means of the Wilhelmy plate method.[30-32] The Wilhelmy plate was either a very thin plate of sandblasted platinum or emery-polished mica. Chromic acid-cleaned petri dishes (30 or 100 cc) were used as troughs and the solutions mixed constantly by magnetic stirring. After the surface was cleaned a Teflon barrier was left at the middle of the trough. Small amounts of concentrated drug were added on the side of the Teflon barrier opposite the Wilhelmy plate. The weight of the meniscus on the Wilhelmy plate was measured with a torsion wire, the sensitivity of which was 42·5 mg/10° of twist. The accuracy of the torsion wire reading

* The compounds in this study were obtained through the courtesy of the following laboratories. Smith, Kline and French: Thorazine (chlorpromazine HCl, MW = 354·5), Temaril (trimeprazine tartrate, MW = 373), Compazine (prochlorperazine ethane disulfonate, MW = 563·5), Stelazine (trifluperazine diHCl, MW = 473), and chlorpromazine sulfoxide HCl, MW = 370·5. Wyeth: Phenergan (promethazine HCl, MW = 320·5), Sparine (promazine HCl, MW = 320), Largon (propriomazine HCl, MW = 376·7), Proketazine (carphenazine maleate, MW = 404), and Equanil (meprobamate): Squibb Institute for Medical Research: Vesprin (trifluprομazine HCl, MW = 388·5) and Prolixin (fluphenazine diHCl, MW = 504. Riker Inc.: butyrylperazine dimaleate, MW = 635. The Schering Corp.: Trilafon (perphenazine). Geigy Pharmaceuticals: Tofranil (imipramine HCl, MW = 316·5). Sandoz Pharmaceuticals, Inc.: Mellaril (thioridazine HCl, MW = 404·5). Wallace: Miltown (meprobamate). Roche Pharmaceuticals: Librium (chlordiazepoxide, MW = 336). Parsidol (ethopropazine HCl, MW = 348), was provided by the Warner-Lambert Research Institute, Research affiliate of Warner-Chilcott Laboratories. Because of low solubility, meprobamate and perphenazine were not studied.

is $\pm 0{\cdot}1°$, and the over-all accuracy is 0·2 dynes/cm. All values reported represent an average of two or three determinations. The temperature was $23 \pm 1°$.

All surface tension measurements were done on a Ringer solution composed of 10 mM sodium phosphate buffer (pH 7·0), 111 mM NaCl, 2·7 mM KCl, and 1·0 mM $CaCl_2$. This solution was used because some of the monolayer work was with frog nerve extract and also because Skou[23–25] used this solution in studying the surface activity of alcohols and anesthetics.

RESULTS

The surface tension of the Ringer solution was $72{\cdot}1 \pm 0{\cdot}2$ dynes/cm. This compares with the accepted value of the surface tension of water which is 72·2 dynes/cm at 23°.

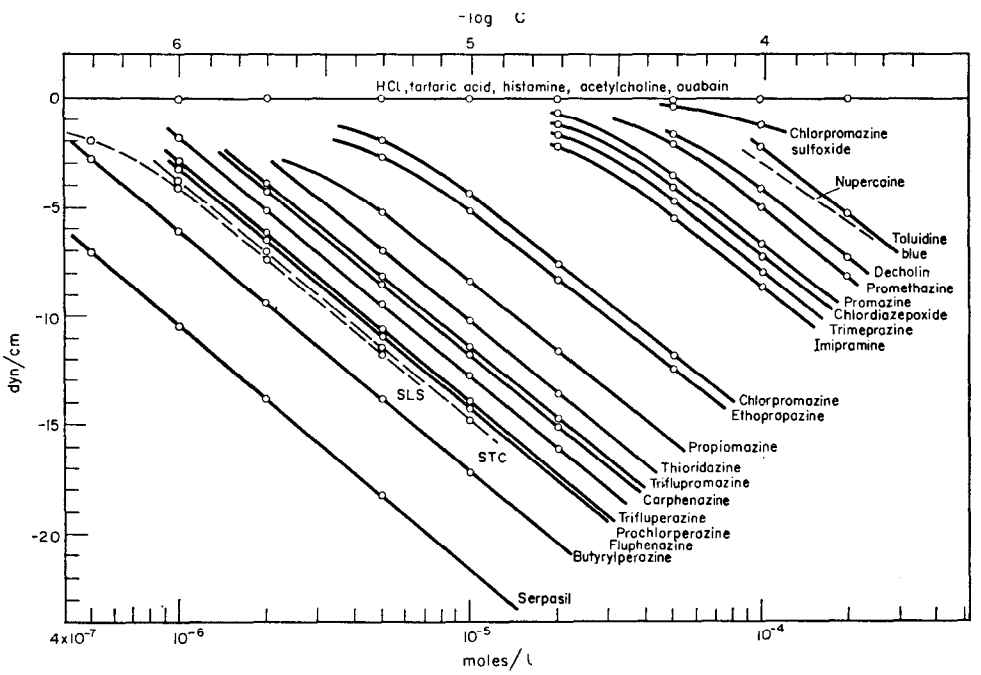

FIG. 1. The drop in surface tension of a Ringer solution (ordinate) is plotted against the solute concentration (lower abscissa; the upper abscissa is log c); 0 represents $72{\cdot}_1$ dynes/cm. Note that the compounds fall into two main groups: the neuroleptics, chlorpromazine to Serpasil, which are very surface active, and the non-neuroleptics which are weakly surface active. SLS is sodium lauryl sulfate and STC is sodium taurocholate. The Nupercaine values are from Skou[23] who found this his most potent local anesthetic.

Figure 1 demonstrates the changes in surface tension observed as the concentration of the compounds is varied . Identical results were obtained whether or not the drug concentration was increased gradually with readings taken after each addition, or increased very rapidly with a highly concentrated amount of drug added at one time.

No change in surface tension was observed with HCl, tartaric acid, citric acid, histamine, acetylcholine, or ouabain (MW = 728·8) up to concentrations of 1 mM. Those compounds that lowered the surface tension did so in an exponential fashion between 5 and 20 dynes/cm (below 72 dynes/cm). These curves thus all fall into

McBain's "type I" surface tension–concentration curves, the commonest variety.[33] Surface tension readings were not taken beyond a fall of 20 dynes/cm. Not shown in Fig. 1 are the values for thionin chloride and methylene blue, both phenothiazine dyes. These fall very near the line for toluidine blue.

Decholin (Ames Co., Indiana) contains 5 mg of sodium citrate for every 200 mg of sodium dehydrocholate. Serpasil injectable (CIBA) contains 0·1 ml dimethylacetamide, 10 mg adipic acid, 0·1 mg Versene, 0·01 ml benzyl alcohol, 0·05 ml polyethylene glycol, 0·5 ascorbic acid, and 0·1 mg sodium sulfite for every 2·5 mg of reserpine (MW = 608). Reserpine phosphate gave values similar to Serpasil. Compazine injectable and prochlorperazine ethanedisulfonate gave identical values even though the former contains 5 mg sodium biphosphate, 12 mg sodium tartrate, 0·9 mg sodium saccharin, and 0·0075 ml benzyl alcohol for every 5 mg of prochlorperazine. The preservatives, therefore, do not greatly affect the surface tension if at all.

For purposes of comparison Fig. 1 also includes the values for Nupercaine as reported by Skou.[23] Skou, working with a similar system, found that Nupercaine was the most potent of the local anesthetics in his series. Sodium lauryl sulfate (Mann Research Laboratory) and impure sodium taurocholate (technical grade, Mann) are also included in Fig. 1.

Because of the fact that these compounds reduce surface tension, it can be said that they adsorb onto the air–water interface (see Discussion).

Compression of the adsorbed films

In order to determine some of the physicochemical characteristics of the adsorbed films, they were compressed by means of a Teflon barrier in a petri dish or a rectangular Langmuir trough with waxed edges.

Figure 2 demonstrates the type of change seen upon the compression of the adsorbed film. When there is no compression a value of approximately 5 dynes/cm is obtained for 10^{-6} M butyrylperazine. This is for a surface area of 22·6 cm^2 (or as will be shown later, 1 molecule per 87 Å^2). The Teflon barrier was quickly pushed, reducing the surface to 19·3 cm^2, and the surface tension dropped instantly from 5 to 9 dynes/cm (below 72 dynes/cm). However, it is seen that over the next 3 min the surface tension rose again slightly. The area was then reduced to 16 cm^2 and a larger transient followed. The largest transient was observed when the area was brought down to 12·7 cm^2. Finally the area was increased by 3 cm^2, and a transient occurred in the opposite direction.

It is felt that these transients represent a desorption of the phenothiazine molecules away from the surface down into the bulk of the solution. This desorption transient will be greater, the greater the surface compression.

An effort was made to spread a monolayer of phenothiazine directly onto the Ringer solution. For this purpose 0·08 ml of a 10^{-4} M solution of the phenothiazine dissolved in 50% ethanol was slowly and carefully dropped onto the surface near the Wilhelmy plate. Spreading occurred rapidly. The magnetic stirrer was not turned on for this experiment. Although enough molecules of phenothiazine had been applied (around 1 molecule/80 to 90 Å^2 of surface), no change in surface tension or surface pressure was recorded as the Teflon bar compressed the surface. It is most likely that, because of the zero bulk concentration, rapid desorption of phenothiazine occurred from the surface.

The liquid nature of the adsorbed film

A bit of talc powder was sprinkled onto the surface of a freshly adsorbed film and a light stream of air directed to the surface. The talc moved very freely, demonstrating that the adsorbed surface film of phenothiazine molecules is very liquid or, rather, having low surface viscosity or rigidity compared for example to a cholesterol–digitonin rigid film. To determine whether the film is liquid-expanded or liquid-condensed would required a pressure–area curve. This was impossible to obtain

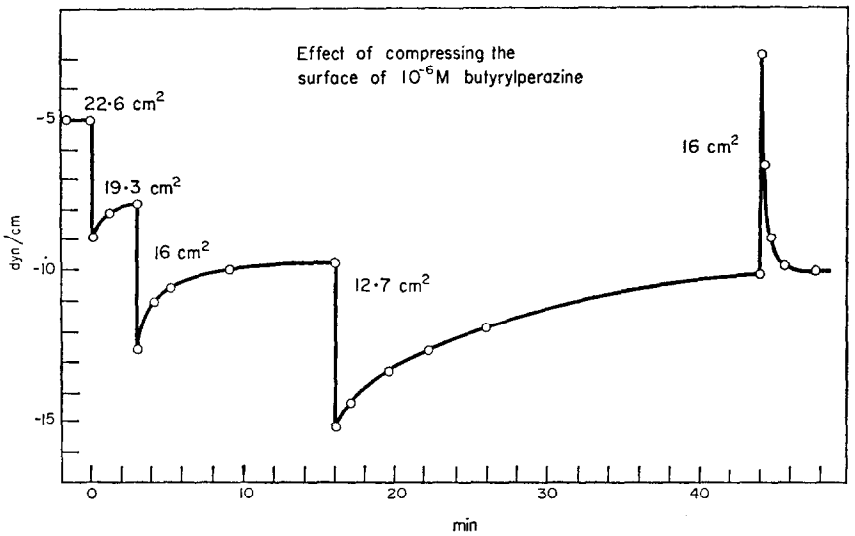

FIG. 2. Demonstrating the changes in surface tension or surface pressure of an adsorbed film of 10^{-6} M butyrylperazine. Reducing the area of the surface causes an instant shift in surface film pressure followed by a transient. The transient represents desorption of butyrylperazine molecules which under pressure leave the surface for the bulk solution. If no surface film existed, then compressing the surface would not change the surface tension at all.

with the present equipment because of the rapid phenothiazine desorption. What is needed is a very rapid compression with an automatic surface pressure recorder so that the pressure–area characteristics can be obtained before appreciable desorption occurs.

Addition of phenothiazines to plasma

The plasma surface tensions of two volunteers and seven acute paranoid schizophrenic patients were measured. These patients were from the Research ward (Dr. Herman C. Denber, Director) of Manhattan State Hospital; 15 ml of blood was mixed with 0·15 ml, containing 150 USP units of sodium heparin, and centrifuged for 20 min at 1,000 × *g*. The plasma was sucked off and the surface tension measured in a beaker 2 hr after the blood was drawn.

The values of the two normal volunteers were 47·0 and 47·0 dynes/cm. The values of the seven schizophrenic patients were 47·1, 47·1, 47·4, 47·4, 47·0, 47·0, 47·0, 47·0. It is seen that all the values are essentially the same, even though some of the patients were taking phenothiazines and some were not. Picon[34] found the surface tension of

normal serum 2 hr after collection to be 47·8 dynes/cm and considered any deviation greater than 1·5 dynes/cm to be pathological.

The addition of chlorpromazine (10^{-4} M) or carphenazine (5×10^{-5} M) to either normal or schizophrenic plasma did not change the surface tension at all. The addition of carphenazine, 6×10^{-5} M, to urine (pH 5) dropped the tension from 44·0 to 41·5 dynes/cm. In the Ringer solution (pH 7) this would have caused a drop of about 22 dynes/cm. Because of the different pH, this comparison is of course not justified.

Effect of adding one drug and then a second

Figure 1 shows that chlorpromazine sulfoxide (1×10^{-4} M) and chlorpromazine (2×10^{-5} M) each separately lowers the tension by 1·5 and 7·5 dynes/cm respectively. However, if one adds chlorpromazine (2×10^{-5} M) after the chlorpromazine sulfoxide has been added, no shift in tension is noted over a period of 10 min. This demonstrates that, although chlorpromazine sulfoxide adsorbs virtually not at all, it is nonetheless effective in retarding the adsorption of chlorpromazine onto the surface. Adding the chlorpromazine sulfoxide after the chlorpromazine does not affect the reading of 7·5 dynes/cm within 10 min.

DISCUSSION

The general observation is that all the neuroleptic compounds studied lower the surface tension of a Ringer solution at very dilute concentrations ranging from 10^{-7} M to 5×10^{-6} M. Figure 1 demonstrates the gap between the neuroleptic drugs and compounds chemically similar but which do not exert a neuroleptic action. These latter mild ataraxics—promazine, chlordiazepoxide, and promethazine—do not appreciably lower the surface tension at concentrations lower than 2×10^{-5} M. Promazine, for example, which differs from chlorpromazine by a chlorine atom, requires 6 times as much drug to produce a drop in surface tension equal to that of chlorpromazine, and requires 27 times as much drug as triflupromazine, from which it differs by a—CF_3 group.

To emphasize the potent nature of these compounds it is interesting to note that in surface activity butyrylperazine and Serpasil both exceed (unpurified) sodium taurocholate (important in digestive emulsification) and sodium lauryl sulfate (a common ingredient of soaps and toothpastes).

In order to see whether the surface activity of the neuroleptic group bore any relation to the clinical efficacy or potency of these compounds, we obtained the average daily clinical dosages from Dr. Herman C. Denber, director of research at Manhattan State Hospital, New York. These dosages are the average ones used by the psychiatric residents on this ward to control the majority of patients in the acute and subacute phases of schizophrenia, predominantly of the paranoid type. Although it would have been desirable to obtain all the dosages for all the drugs from a single ward where the physicians use a relatively constant, although arbitrary, set of "antipsychotic criteria," it was not possible to obtain dosages from this ward for every drug. The daily dosage for one of these neuroleptics, therefore, came from the pharmaceutical manufacturer's recommendations (*Physicians' Desk Reference*).

The average daily clinical controlling doses obtained from these two sources are as follows: Serpasil 1–2 mg; butyrylperazine 5–20 mg; fluphenazine 15–50 mg; prochlorperazine 45–90 mg; trifluperazine 30–75 mg; carphenazine 75–150 mg;

triflupromazine 100–150 mg; thioridazine 100–300 mg; ethopropazine 200–400 mg; chlorpromazine 300–600 mg. These doses agree fairly well with the *midrange* doses listed by Kapp and Gottschalk[35] who actually recorded the extreme ranges used by different groups of psychiatrists for different diagnostic categories of both psychotic and psychoneurotic patients.

These doses have been converted into micromoles (see values for molecular weights in Materials and Methods) and plotted against the concentration of the drug that lowers the surface tension by 5 dynes/cm, an arbitrarily selected value. This is shown in Fig. 3, where the solid black bars represent the range of each dose. The diagonal

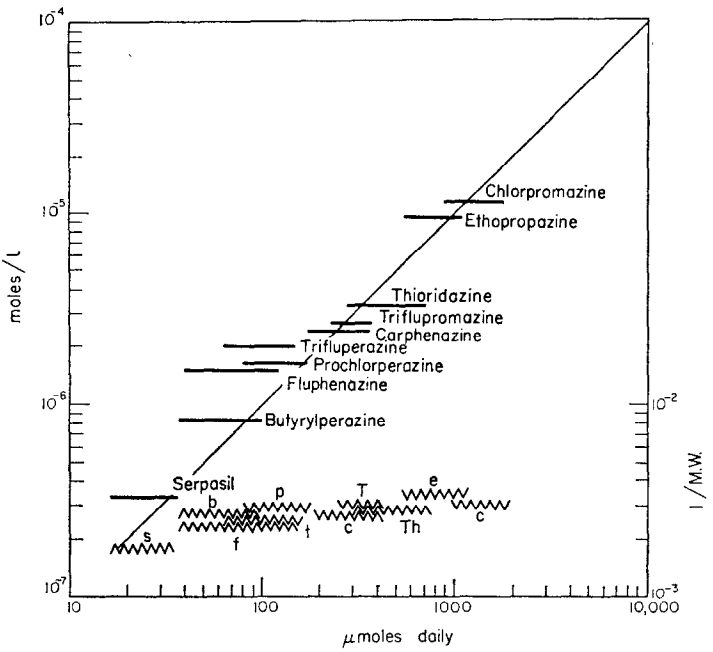

FIG. 3. Demonstrating a correlation between surface activity and clinical activity. The concentration of drug that lowers the surface tension by 5 dynes/cm is on the ordinate. The abscissa represents the average dose range used to control acute paranoid schizophrenia by one group of physicians on one hospital ward. The solid black bars indicate the surface activity, and the wavy lines represent the inverse of the molecular weight. The straight line is the theoretical line for an exact 1:1 correlation. It is seen that a 100-fold increase in surface activity is approximately associated with a 100-fold decrease in the daily oral dose in micromoles.

line represents the 1:1 theoretical correlation. It is seen that a 100-fold increase in surface activity is roughly matched by a 100-fold increase in clinical potency. In this same figure is plotted the inverse of the molecular weights of the compounds. A definite small correlation is noted, but this represents only a 2-fold rise in molecular weight for a 100-fold rise in clinical potency. The oil/water solubility coefficients remain to be determined and correlated.

A correlation between phenothiazine clinical potency and the degree of immobilization of *Tetrahymena pyriformis* has been obtained by Guttman and Friedman.[36]

These workers found that the drugs were active in the following order: trifluperazine, prochlorperazine, perphenazine, fluphenazine, thioridazine, triflupromazine, chlorpromazine, acetophenazine, promazine, and promethazine, the first-mentioned drug being the most potent. Since no concentration values were mentioned in their brief abstract it is difficult to compare data closely.

On the other hand, the non-neuroleptic compounds in Fig. 1 do not, as a group, show any correlation to clinical effect. Imipramine (a clinical "antidepressant",[7] trimeprazine and promethazine (antihistamines primarily), and promazine all give values roughly in the same region, despite their very different clinical effects. Chlorpromazine sulfoxide,clinically ineffective as an antipsychotic neuroleptic, is also very ineffective in lowering the surface tension, doing no better than the phenothiazine dye, toluidine blue. It is also seen that the local anesthetics, Nupercaine, tetracaine, and others, as reported by Skou,[23] are much less surface active than the neuroleptic drugs.

Physicochemical interpretations

According to what is known of the physics of surfaces, the lowering of surface tension is a manifestation of solute adsorption at the interface.[32] The fact that these neuroleptics do indeed form an adsorbed film at the surface is demonstrated by the compression type of experiment in Fig. 2. If these molecules did not accumulate or adsorb onto the surface then compression would not have changed the surface tension at all.

In order to calculate how many molecules were adsorbed onto the surface the Gibbs adsorption theorem was used.[32, 33]

$$n = -\frac{c(dg/dc)}{kT} = -\frac{0{\cdot}43_5}{kT}\frac{dg}{d\log c}$$

where n is the number of solute molecules adsorbed per cm^2 of surface, k is the Boltzmann constant ($1{\cdot}38 \times 10^{-16}$ erg/degree), T is the absolute temperature (296 °K at room temperature, 23 °C), c is the solute concentration in moles/l, g is the surface tension in dynes/cm, and dg/dc is the slope or rate of variation of surface tension with concentration.

Because all the lines in Fig. 1 are nearly parallel the value $-c(dg/dc)$ [or $-0{\cdot}43_5(dg/d\log c)$] is the same for all the compounds (except chlorpromazine sulfoxide) and is $4{\cdot}7_2$ dynes/cm. Hence n is $1{\cdot}1_5 \times 10^{14}$ molecules per cm^2 of surface, or 1 molecule per 87 Å^2. According to Davies and Rideal,[32] the majority if not all of these adsorbed molecules reside within the first 10 to 50 Ångstroms below the surface. Moreover, since the limiting van der Waals outline of the phenothiazine ring has an area of about 60 Å^2 (as determined with Godfrey molecular models), it seems that the composition of the surface is virtually a monomolecular layer of solute.

The surface concentration, C_s, can be calculated by the equation of Davies and Rideal:[32] $C_s = n/d$, where d is the thickness of the adsorbed layer in Ångstroms. The length of the piperizinated phenothiazines, trifluperazine, prochlorperazine, butyrylperazine, etc., is of the order of 17 to 19 Å long (Godfrey models). For a d value of 20 Å, C_s is of the order of 1 M, which is from 100,000 to 1,000,000 times the concentration in the bulk solution.

Despite this high surface concentration, the total number of molecules that actually leave the bulk phase to form the surface film is only about 1% of the number of molecules in the bulk—in other words, as the surface film is being formed, the bulk concentration falls by about 1%. The more dilute the solution, then, the more the bulk concentrations will fall; solutions more dilute than 10^{-7} M should therefore be re-examined with the area of the trough kept as small as possible and the bulk as large as feasible.

The film-compression studies demonstrate that we are not dealing here with solutes, which, once adsorbed, do not desorb back into the bulk phase. The transients of Fig. 2 are best interpreted as desorption transients as the film pressure is increased. The energy of desorption, therefore, is not infinitely high and may be calculated by equation 4.1 of Davies and Rideal:[32]

$$L = RT \ln \frac{C_s}{C_b}$$

where L is the energy of desorption, R is the gas constant (1·987(calories/°K − mol) T is 296 °K, C_s is the surface concentration and C_b is the bulk concentration. For a C_s/C_b ration of 10^5 to 10^6, L is around 7,000 to 8,000 calories/mole.

Biological implications

It is interesting to compare the air–water adsorption reported above with the adsorption of these phenothiazines onto erythrocytes. Freeman and Spirtes[10] found that 0·1 ml human blood in 10 ml of $2{\cdot}5 \times 10^{-5}$ M trifluperazine quickly adsorbed 26% of the drug. This amounts to about 1 molecule per 185 Å^2 of red-cell surface and compares with the Ringer adsorption of trifluperazine which was 1 molecule per 87 Å^2 of interface.

It was seen, therefore, that over twice as many molecules adsorb onto the air–Ringer interface than onto the erythrocyte–water interface. This implies that some or possibly all of the phenothiazine adsorption onto tissue cells may be explained by the physical chemistry involved in air–water adsorption. Although the absolute amounts of various phenothiazines adsorbed by tissue cells will in general be different from the air–water adsorption, Lewis[37] has stated that "the *order* in which a series of dissolved substances are adsorbed does not differ even when one substitutes as the adsorbing material unlike bodies." In addition to this adsorption, phenothiazine–lipid complexes must occur,[38] and it is conceivable that partial penetration occurs between the lipid molecules of the cell membrane, thereby decreasing membrane permeability. This has been demonstrated by Skou[24, 25] for alcohols and anesthetics on frog nerve-membrane extracts.

It has been found[39, 40] that membrane stabilizers, such as cocaine and procaine, can affect the membrane permeability "apparently by formation of a diffusion-limited subfilm"[40] on the outer aspect of the cell membrane. We feel that neuroleptic compounds fall into this category of stabilizers in that they form virtually monomolecular films around the cell membrane and reduce transmembrane permeability to practically all solutes, as outlined in the introduction of this article. Certainly the phenomenon of surface accumulation or adsorption of phenothiazine would result in marked

changes in any enzyme that resided on the surface of the cell membrane. The phenothiazine ring is the oil-soluble portion of the molecule and so will adsorb onto the membrane, while the side chain is hydrophilic and hangs down into the water phase. The film essentially adds another 15 to 20 Å to the thickness of the cell membrane and in this way might easily reduce permeability in general.

Because of the potent surface activity of these compounds, it is not surprising that high concentrations would cause lysis of the cell membranes by emulsification and micelle formation. This has been reported by Freeman and Spirtes,[41] who found hemolysis with chlorpromazine above 10^{-4} M, and Spirtes and Guth[5] who observed mitochondrial lysis at 4×10^{-4} M. In general, however, it has been demonstrated that there is no simple correlation between lytic activity of a substance and its ability to lower the surface tension.[42]

In conclusion, the rough correlation demonstrated in Fig. 3 implies that possibly all neuroleptics will lower surface tension in proportion to their clinical potency. It remains to be seen whether a nontoxic substance such as sodium dehydrocholate[43] may be clinically effective if given in high enough concentration to form an adsorbed film. The measurement of surface activity might be useful as a quick, preliminary, empirical screening method in the search for new, more effective, and safer antipsychotic compounds. It would be interesting to examine different groups of tranquilizers—for example, the β-amino ketones.[44] Finally, extracts of excitable membranes should be tested to see whether film penetration by these compounds occurs.

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