In Vitro Interaction of Neuroleptics and Tricylic Antidepressants with Coffee, Tea, and Gallotannic Acid

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Abstract □ The *in vitro* interaction of selected drugs with coffee, tea, gallic acid, and gallotannic acid was examined by mixing solutions of drug with each of these four preparations. Results of these experiments indicate that significant precipitation occurs for a variety of agents, including several phenothiazines, amitriptyline, haloperidol, imipramine, and loxapine. The strong complex which is formed between these drugs and tannins is probably the basis of the interaction of these drugs with coffee and tea. Although precipitates did occur with a number of neuroleptics, two members of this drug class, thiothixene and molindone, failed to interact with the solutions used.

Keyphrases □ Tricyclic antidepressants—*in vitro* interaction with coffee, tea, gallotannic acid, and gallic acid □ Neuroleptics—*in vitro* interaction with coffee, tea, gallotannic acid, and gallic acid

The interaction of certain antipsychotic agents with tea and coffee has received some attention in recent years. Mikkelsen (1) first reported that increased consumption of coffee may reduce the effectiveness of phenothiazines. Soon after, Hirsch (2) and Kulhaneck *et al.* (3) reported that *in vitro* mixing of a number of neuroleptics, including chlorpromazine, haloperidol, and fluphenazine (but not trifluoperazine), with coffee or tea led to the formation of a precipitate. Cheeseman and Neal (4) have studied the interaction of chlorpromazine with coffee and tea in more detail and have found that simultaneous oral administration of tea with chlorpromazine completely abolished the cataleptic effects of this drug in rats. Concern about the possible effects which precipitation of antipsychotics could have on their bioavailability in humans led Bowen *et al.* (5) to study the possible interaction of coffee and tea with these four drugs in female patients. Using a dopamine receptor assay (6), plasma drug concentrations were measured during sequential weekly periods of normal coffee and tea intake, abstinence from these beverages, and finally resumption of intake. On the basis of plasma drug levels and behavioral scores (7), they concluded that withdrawal of coffee and tea did not increase drug bioavailability. However, neither the amounts of coffee and tea used in this study nor the timing of beverage intake with respect to drug administration were specified. Furthermore, the time intervals used in the overall design of this experiment were questionable.

In the present study, we report results on the *in vitro* interaction of coffee, tea, gallotannic acid, and gallic acid with a variety of neuroleptic agents, as well as amitriptyline and imipramine.

EXPERIMENTAL SECTION

The drugs used in this study included amitriptyline hydrochloride[1], chlorpromazine hydrochloride[2], haloperidol[3], imipramine hydrochloride[2], loxapine hydrochloride[4], molindone hydrochloride[5], prochlorperazine hydrochloride[6], thioridazine hydrochloride[7], thiothixene hydrochloride[8], and trifluoperazine hydrochloride[2]. Gallotannic acid[9] and gallic acid[2] were commercially obtained. The buffer solutions used in these studies were McIlvaine's buffer (0.1 M citric acid–0.2 M sodium dihydrogen phosphate, pH 2–8) and Clark and Lub's buffer (0.1 M potassium chloride–0.1 M hydrochloric acid, pH 1).

pH Variability Studies—Portions (1 mL) of an aqueous solution of drug (20 mg/mL) were diluted with 1 mL of buffer. This solution was then added to a mixture of aqueous gallotannic acid (1 mL, 20 mg/mL) and buffer (3 mL) to achieve final concentrations of drug and gallotannic acid of 3.3 mg/mL each. The resulting precipitate was removed by filtration[10]. A portion of the filtrate (2 mL) was acidified by the addition of 2 M HCl in a dropwise manner and adjusted to pH 2 by addition of 2 mL of buffer. A saturated solution of lead acetate (2 mL) was added to the acidified filtrate, and the resulting precipitate was removed by filtration. The concentration of free drug in the filtrate was determined by comparing the UV absorbance of appropriately diluted samples with a standard curve of absorbance *versus* concentration. Experiments designed to study the interaction of gallotannic acid with various drugs at specific pH values were carried out in an identical manner. Studies assessing the effects of reduced drug concentration on precipitation were also carried out in an identical fashion with drug concentrations of 2 mg/mL (for a 1:10 dilution). Samples containing drug at a 1:10 dilution required an additional extraction step because of the high concentration of tannin relative to drug. During this step, 2 mL of the lead acetate filtrate was adjusted to pH 10 by addition of 1 M NaOH in a dropwise manner. This solution was then extracted three times with 2-mL portions of distilled ethyl acetate. The combined ethyl acetate fractions were washed with water, dried with anhydrous sodium sulfate, filtered, and evaporated. The remaining residue was dissolved in 4 mL of buffer (pH 2) before dilution and UV absorption measurement.

Studies to estimate the effects of mutual dilution of drug and tannin were conducted by using buffered solutions of drug and gallotannic acid which were diluted 1:5 with distilled water before mixing and filtration. The filtrate (2 mL) was then mixed with 2 mL of buffer (pH 2), treated with 2 mL of lead acetate, and filtered before UV absorption measurements.

Experiments with Coffee and Tea—Measurements of the interaction of coffee and tea with neuroleptic agents were carried out by mixing aqueous solutions of drugs with these beverages in the following proportions: for amitriptyline, haloperidol, and loxapine, 1 mL of drug solution (10 mg/mL) with 2.5 mL of beverage; for thiothixene, 1 mL of drug solution (5 mg/mL) with 0.65 mL of beverage. All other studies were conducted with 1 mL of drug solution (20 mg/mL) and 5 mL of beverage. Coffee was prepared by dissolving 2 g of instant coffee in 150 mL of boiling distilled water. Tea infusions were prepared by steeping one tea bag containing 2.5 g of black tea in 150 mL of boiling water for 5 min. The pH resulting from addition of drug to tea or coffee varied between 4.5 and 5.0. In the experiments with tea, the resulting precipitates were filtered, and 2-mL portions of the filtrate were diluted with buffer, treated with lead acetate, and filtered as described above. In the experiments with coffee, the drug precipitates and lead–tannin precipitates were removed by centrifugation at 4000 rpm for 8 min. Extractions and UV absorption measurements were then carried out as described above.

Other Studies—Studies designed to examine the reversibility of the interaction between chlorpromazine and gallotannic acid in an aqueous medium were conducted by mixing buffered (pH 5) solutions of drug and gallotannic acid as described above. The resulting suspension was placed in a dialysis bag made from benzoylated dialysis tubing[2] (exclusion range, 1200–2000). The bag was immersed in four volumes of buffer and stirred at room temperature for 24 h. The suspension within the dialysis bag was then filtered. Portions of this filtrate, as well as the dialysate, were then treated with lead acetate, filtered, and diluted in preparation for the UV absorption measurement. The

[1] Merck, Sharp and Dohme Co.
[2] Sigma Chemical Co., St. Louis, Mo.
[3] McNeill Laboratories, Inc.
[4] Lederle Laboratories.
[5] Endo, Inc.
[6] Smith Kline and French Laboratories.
[7] Sandoz Pharmaceuticals.
[8] Roerig.
[9] FCC grade; J.T. Baker Chemical Co.
[10] Whatman no. 1.

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Table I—Interactions of Neuroleptics and Antidepressants with Gallotannic Acid, Tea, Coffee, and Gallic Acid [a]

Drug [b]	Percent Drug Precipitated by Gallotannic Acid [c]		Percent Drug Precipitated by Tea		Percent Drug Precipitated by Coffee	Drug-Gallic Acid [d] Interactions
	20 mg/mL	2 mg/mL	20 mg/mL	2 mg/mL		
Amitriptyline hydrochloride (245 nm)	43 ± 2 (5)	nd [e]	12 ± 1	nd	nd	nr [f]
Chlorpromazine hydrochloride (305 nm)	91 ± 1 (6)	69 ± 1	51 ± 2	69 ± 1	19 ± 2	+
Haloperidol hydrochloride (252 nm)	41 ± 4 (6)	nd	3 ± 1	nd	nd	nr
Imipramine hydrochloride (252 nm)	64 ± 1 (6)	54 ± 1	62 ± 1	nd	nd	nr
Loxapine hydrochloride (295 nm)	80 ± 5 (6)	72 ± 4	nd	nd	nd	nr
Molindone hydrochloride	nr	nr	nr	nr	nr	nr
Prochlorperazine hydrochloride (305 nm)	98 ± 1 (5)	84 ± 1	84 ± 1	94 ± 1	65 ± 1	+
Thioridazine hydrochloride (312 nm)	91 ± 1 (4)	76 ± 2	71 ± 1	78 ± 1	55 ± 1 [g]	+
Thiothixene	nr	nr	nr	nr	nr	nr
Trifluoperazine hydrochloride (305 nm)	88 ± 1 (6)	61 ± 1	51 ± 2	80 ± 1	31 ± 1	+

[a] Values listed are averages of triplicate determinations taken at drug concentrations of 20 and 2 mg/mL. [b] Numbers in parentheses indicate wavelengths at which measurements were made. [c] Numbers in parentheses indicate pH vaues at which these determinations were made. The pH values represent the highest pH which could be used without precipitating the free base forms of these drugs. [d] All determinations were made with pH 5 buffer. [e] nd—Percent drug precipitated was not determined due to weak drug absorptions and interfering absorptions due to constituents in coffee and tea. In the case of loxapine, measurements were not made due to inability to extract drug into the organic phase. [f] nr—No precipitate was formed on mixture of these substances. [g] Duplicate experiments indicated that 67% drug precipitation occurred when the same brand of decaffeinated coffee was mixed with thioridazine.

resulting absorbances for these fractions were compared with those obtained from a dialysis experiment using chlorpromazine alone, which was dissolved in buffer (pH 5). A similar procedure was used to examine the reversibility of the interaction between chlorpromazine and the condensed tannins present in tea. A solution of drug and tea were mixed as described above, and this mixture was placed in a dialysis bag which was immersed in water for 24 h with stirring.

In a separate experiment, a buffered solution of chlorpromazine was mixed with tea or gallotannic acid. A portion of the resulting suspension was centrifuged at 4000 rpm for 8 min. The supernatant was decanted, and the remaining pellet was washed by resuspending in distilled water and centrifuging. After decanting the resulting supernatant, the drug precipitate was washed once more and then dissolved in 6 mL of a 1:1 methanol-water. Several drops of this solution were treated with 3% ferric chloride in 0.5 M HCl. Another portion of this solution was spotted on a TLC plate[11], which was developed in methanol and visualized under short-wavelength UV light.

RESULTS AND DISCUSSION

In Table I the interactions which occurred between the various drugs and the solutions are listed. Although drug precipitation was most pronounced with phenothiazines, it also occurred with other drugs as well. The observation of precipitate formation between trifluoperazine and coffee or tea is contrary to the results reported by Hirsch (2).

It is not surprising that tannins interact with many of the drugs examined in this study. Both hydrolyzable tannins (*e.g.*, gallotannic acid) and condensed tannins, such as those present in tea and coffee, are known for their ability to precipitate metals, proteins, and certain organic compounds (8–10). The historic use of gallotannic acid as an antidote for alkaloid poisoning is based on its ability to form precipitates with many such natural products (11). Gallotannic acid complexes with morphine and cyanocobalamin have been examined as possible sustained dosage forms (12, 13). The effects of tannins on the absorption of iron and thiamine have also been studied. Roy and Mukherjee (14) have studied the effects of food tannins on iron metabolism. Morck *et al.* (15) have recently demonstrated that both coffee and tea can inhibit iron absorption in humans. In studies of the interaction between gallotannic acid and thiamine (16), it has been suggested that excessive intake of tea can contribute to thiamine deficiency, possibly because the phenolic groups of the tannins found in tea participate in ring opening and oxidation reactions of thiamine (17).

The phenothiazines used in these studies formed a precipitate with gallic acid, which is a constituent of both condensed and hydrolyzable tannins. Cheeseman and Neal have reported precipitation of chlorpromazine with solutions of sodium benzoate and sodium salicylate (4). They have suggested that these agents could account for the observed interactions of neuroleptics with coffee and tea. However, the concentrations of the aromatic acids used in the studies of Cheeseman and Neal, as well as the gallic acid solutions used in this study, are much higher than those which could exist in coffee and tea. On the other hand, the concentrations of tannins found in tea are high enough to account for the degree of drug precipitation seen in Table I. The differences in the amounts of drug precipitated by coffee and tea reflect the differences in tannin content (tea, 10–15%; coffee, 3–5%). In addition, ferric chloride treatment of a washed chlorpromazine–tea precipitate resulted in the production of a dark-green color, which is indicative of polyphenolic compounds, such as the condensed tannins present in tea. Furthermore, tea which was pretreated with lead acetate to remove tannins failed to produce a precipitate when mixed with chlorpromazine.

Experiments were carried out by using thioridazine with regular and decaffeinated coffee to test the possible effects of caffeine on drug precipitation. The results show very little difference in the amount of drug precipitated with the two varieties of coffee. Thus, any competition which may exist between caffeine and drug in complexing with tannins results in a minimal decline in drug precipitation. Although caffeine may not alter drug precipitation in tea or coffee, it could exert significant influence on the therapeutic effects of phenothiazines by producing pharmacokinetic or pharmacodynamic interactions. Such interactions may result from effects of caffeine on microsomal metabolism of antipsychotics (18) or from possible pharmacological antagonism (19). Evidence for a pharmacological effect is conflicting. Morpurgo (20) has reported that caffeine citrate (10 mg/kg) totally inhibited the cataleptic effects of phenothiazines in rats within 1 h after administration. On the other hand, Cheeseman and Neal have found that the caffeine content in tea did not account for the total loss of chlorpromazine-induced catalepsy in rats when tea was administered simultaneously (4). The doses of chlorpromazine and caffeine used in this experiment were 8 and 15 mg/kg, respectively.

The effects of pH and dilution on drug precipitation were studied in some detail to learn more of the drug-tannin interaction. The results shown in Fig. 1 indicate that the percent precipitation of imipramine, loxapine, and thioridazine increases as the pH increases from 1 to 6. A similar trend holds for all other drugs listed in Table I when mixed with either gallotannic acid or tea. Furthermore, dilution studies indicate that a significant amount of chlorpromazine (59%) is precipitated, even when drug and gallotannic acid are both diluted 1:5 before mixing. Experiments with tea and chlorpromazine diluted 1:5 resulted in a 36% drug precipitation. As indicated in Table I, a 10-fold dilution of drug alone also had little effect on total drug precipitation. Such increases in drug precipitation which occur with dilution are consistent with the results of Cheeseman and Neal (4), who have reported increases in percent chlorpromazine precipitation as the chlorpromazine–tea ratio is reduced.

Additional experiments have indicated that the drug-tannin complex is strong in the sense that the majority of drug remains complexed with tannin after prolonged dialysis. Dialysis of the chlorpromazine–gallotannic acid precipitate at pH 5 for 24 h showed that 90% of total drug remained complexed. Dialysis of a chlorpromazine–tea precipitate showed that 62% of the drug remained complexed after 24 h. However, although the complex between chlorpromazine and tannins is strong, it is not irreversible, and it does not produce a modification of the drug molecule. Dissolution of the precipitate in methanol–water (1:1), followed by TLC showed the presence of chlorpromazine. This result is in agreement with the findings of Kulhaneck *et al.* (3), who have reported that fluophenazine and haloperidol were liberated unchanged by dissolving drug–tea precipitates in water.

CONCLUSIONS

The present studies identify tannins as the major contributory factor in the precipitation of various neuroleptics and tricyclic antidepressants by coffee and tea. They also indicate that tea and coffee can precipitate significant

[11] Silica gel 60 F-254.

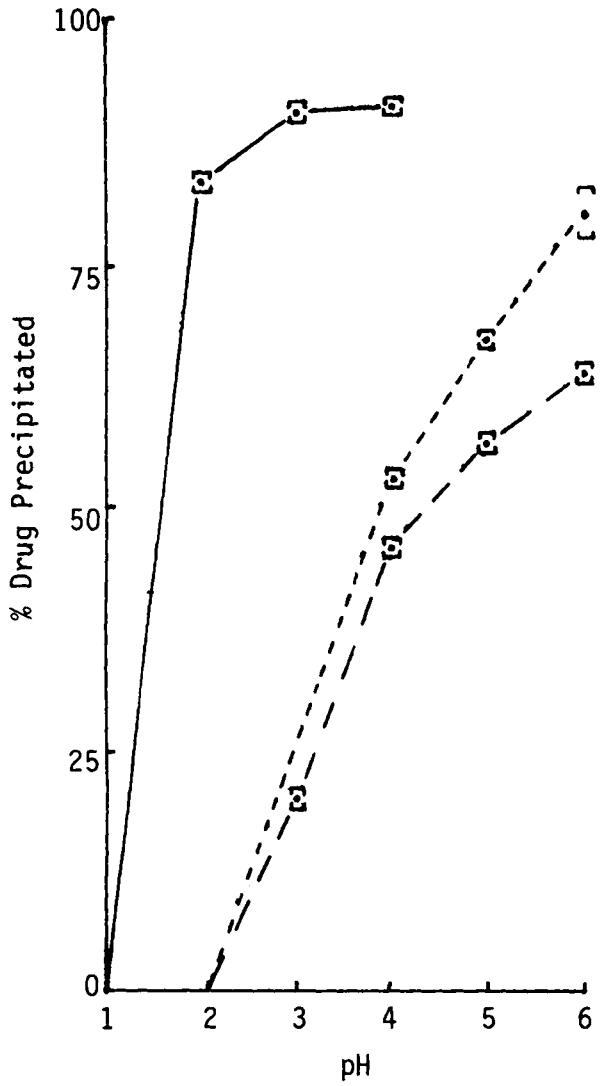

Figure 1—*pH variability of drug-gallotannic acid interaction. Plots represent results with thioridazine (—), loxapine (- - - -), and imipramine (— —). Each point represents the average of three determinations. At pH 3, loxapine produced a fine precipitate which could not be isolated by filtration or centrifugation. However, no precipitate was formed with this drug at pH 2.*

amounts of these drugs, especially phenothiazines. It is possible that the effects of gastric acidity, along with GI secretions and motility, may drastically reduce the amount of drug complexed in the intestine. However, studies on the effects of pH and dilution indicate that any drug-tannin complexation which may occur in the GI tract should be maximal in the intestine, where most drug absorption occurs. Furthermore, dilution studies indicate that gallotannic acid and tea precipitate significant amounts of drug even at somewhat diluted concentrations, suggesting that dilution in the intestine may not completely eliminate drug-tannin interactions. Finally, dialysis experiments show that the chlorpromazine-gallotannic acid complex is quite stable at nearly neutral pH. Thus, once formed, the drug-tannin precipitate may not be readily soluble in the intestine.

Studies in rats have shown that simultaneous administration of tea can abolish the cataleptic effects of chlorpromazine. Whether this effect is due to caffeine or other components in tea is open to question. Bowen *et al.* (5) have reported that abstinence from tea or coffee had no effect on the bioavailability of several neuroleptics studied. However, the time and amounts of coffee and tea intake in this study were not specified. It is interesting to note that Bogner and Walsh (21) have compared the absorption of a sustained-release complex of gallotannic acid and radiolabeled phenylephrine hydrochloride with that of phenylephrine hydrochloride alone in human volunteers. The results indicated that use of the drug-tannin complex prolonged the time at which peak radioactivity was observed in the blood and reduced levels of peak radioactivity. A reduction in total radioactivity *versus* time (~25%) also occurred during the 24-h period in which measurements were taken. Prolonged absorption such as that observed in this study may have an especially significant role in affecting blood and tissue levels of drugs, such as chlorpromazine, which undergo significant metabolism in the intestine (22, 23). More detailed studies need to be carried out on the possible *in vivo* interaction of coffee and tea with neuroleptics and tricyclic antidepressants.

REFERENCES

(1) E. J. Mikkelsen, *J. Clin. Psychiat.*, **39**, 732 (1978).

(2) S. R. Hirsch, *Lancet*, **ii**, 1130 (1979).

(3) F. Kulhaneck, O. K. Linde, and G. Meisenberg, *Lancet*, **ii**, 1130 (1979).

(4) H. J. Cheeseman and M. J. Neal, *Br. J. Clin. Pharm.*, **12**, 165 (1981).

(5) S. Bowen, K. M. Taylor, and I. A. McI. Gibb, *Lancet*, **i**, 1217 (1981).

(6) I. Creese and S. H. Sander, *Nature (London)*, **270**, 180 (1977).

(7) K. Nihira, R. Foster, M. Shellhaas, and H. Leland, "AAMD Adaptive Behavior Scale Manual," American Association of Mental Deficiency, Washington, D.C., 1975.

(8) E. Haslam, "The Chemistry of Vegetable Tannins," Academic, New York, N.Y., 1966.

(9) M. E. Wall, H. Taylor, L. Ambrosio, and K. Davis, *J. Pharm. Sci.*, **58**, 839 (1969).

(10) N. Kojima, D. Wallace, and G. W. Bates, *Am. J. Clin. Nutr.*, **34**, 1392 (1981).

(11) "U.S. Dispensatory," 25th Ed., Lippincott, Philadelphia, Pa., 1955, pp. 1379–1380.

(12) B. Brands, J. C. Baskerville, R. Herve, M. Hirst, and C. W. Gowdey, *Neuropharmacology*, **19**, 443 (1980).

(13) K. Kristensen and T. Hansen, *J. Pharm. Sci.*, **55**, 610 (1966).

(14) S. N. Roy and S. Mukherjee, *Ind. J. Biochem. Biophys.*, **16**, 93 (1979).

(15) T. A. Morck, S. R. Lynch, and J. D. Cook, *Am. J. Clin. Nutr.*, **37**, 416 (1983).

(16) K. Rungravngsak, P. Tosukhoweng, B. Panjipan, and S. L. Vimakesani, *J. Am. Diet. Assoc.*, **30**, 1680 (1977).

(17) B. Panjipan and K. Ratanaubalchai, *Int. J. Vit. Nutr. Res.*, **50**, 247 (1980).

(18) C. Mitoma, T. J. Sorich, and S. Neubauer, *Life Sci.*, **7**, 145 (1968).

(19) F. A. Freyhan, *Am. J. Psychiat.*, **115**, 577 (1959).

(20) C. Morpurgo, *Arch. Int. Pharmacodyn.*, **137**, 84 (1962).

(21) R. L. Bogner and J. M. Walsh, *J. Pharm. Sci.*, **53**, 617 (1964).

(22) L. Rivera-Calimlim, L. Castanneda, and L. Lasagna, *Clin. Pharmacol. Ther.*, **14**, 978 (1973).

(23) S. H. Curry, A. D'Mello, and G. P. Mould, *Br. J. Pharmacol.*, **42**, 403 (1971).

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