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THIORIDAZINE-FLUOXETINE INTERACTION AT THE LEVEL OF THE DISTRIBUTION PROCESS *IN VIVO*

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The aim of the present study was to investigate the effect of the distribution interaction between thioridazine and fluoxetine *in vivo*. Experiments were carried out on male Wistar rats. Animals received thioridazine and fluoxetine separately or jointly, at a dose of 10 mg/kg *ip*. Concentrations of thioridazine and its metabolites and fluoxetine in the plasma and tissues were measured at 1 h after administration of the drugs (HPLC). Effects of distribution interactions were estimated on the basis of the calculated tissue/plasma and lysosome-poor/lysosome-rich tissue concentration ratios, considering the heart and muscles as lysosome-poor tissues and the lungs, liver and kidneys as lysosome-rich ones.

Fluoxetine diminished the tissue/plasma concentration ratio of thioridazine for the lungs, but elevated this ratio for the muscles and heart. On the other hand, thioridazine elevated the brain/plasma and heart/plasma concentration ratios of fluoxetine. Consequently, the thioridazine lysosome-poor/lysosome-rich tissue concentration ratios significantly increased in the presence of fluoxetine. At the same time, thioridazine raised (or showed such a tendency) the heart/lysosome-rich tissue concentration ratios of fluoxetine, not changing significantly the muscles/lysosome-rich tissue concentration ratios of the antidepressant.

The presented results provide evidence that the distribution interactions between thioridazine and fluoxetine observed *in vitro* occur also *in vivo*, leading to a shift of the drugs from organs rich in lysosomes to those poor in these organella, in particular to the heart. Thioridazine and fluoxetine mutually increased their heart/plasma and heart/lysosome-rich tissue concentration ratios, i.e. the heart/lung, heart/liver and heart/kidneys ratios. Similar results were obtained with lysosome-poor muscles in the case of thioridazine. The obtained results confirm that, apart from the lysosome density in the investigated tissues, the potential metabolic interactions in the liver and the pattern of drug circulation in a body have an important impact on the calculated drug concentration ratios. Moreover, considering serious side-effects of thioridazine (cardiotoxicity, anticholinergic activity), the administration of thioridazine-fluoxetine combination studied herein should be approached with caution, considering appropriate dose adjustment.

Key words: *thioridazine, fluoxetine, lysosomal trapping, distribution interaction*

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INTRODUCTION

Thioridazine, a piperidine-type phenothiazine neuroleptic, is a mild neuroleptic which acts on both positive and negative symptoms of schizophrenia, displaying sedative and some antidepressant effects. The main side-effects of thioridazine are connected with its influence on cardiac muscle conduction and anticholinergic activity. In comparison with other neuroleptic drugs, thioridazine produces more distinct ECG abnormalities which are dose-dependent [1, 17, 24]. Because of its psychotropic profile, the drug is suitable for being combined with antidepressants in the therapy of many psychiatric disorders (psychotic depression, "treatment-resistant" depression, depression in the course of schizophrenia, schizoaffective psychosis).

Joint administration of phenothiazine neuroleptics and selective serotonin reuptake inhibitors (SSRIs) results in the pharmacokinetic interactions which in turn lead to the increased plasma and tissue concentrations of the drugs in humans and rats [6, 7, 9, 25, 27]. These interactions are attributed to competitive inhibition of the drug metabolism at a level of cytochrome P-450. SSRIs are known as inhibitors of cytochrome P-450 isoenzymes [3, 4, 18]. However, our recent investigations suggest that the observed pharmacokinetic interactions between SSRIs and neuroleptics may also take place at a level of drug distribution, since both phenothiazine neuroleptics and SSRIs are basic lipophilic drugs [11–13].

Basic lipophilic compounds are characterized by a high volume of distribution as a result of extensive tissue uptake. The main mechanisms of such a distribution pattern seem to be the non-specific binding to membrane phospholipids [2, 16, 19, 23], and the trapping by acidic subcellular compartments, mainly lysosomes [5, 20, 21]. Our recent findings have shown that the tissue distribution of fluoxetine (SSRI) depended on phospholipid binding rather than on lysosomal trapping [10], whereas in the case of thioridazine lysosomal trapping was as important for the tissue uptake as was phospholipid binding [13].

After permeating through the lysosomal membrane, weak bases dissociate in the acidic interior of lysosomes, becoming unable to diffuse back into the cytosol and, thus, raising the vesicular pH [15, 22]. When two basic lipophilic drugs are trapped by lysosomes, the internal acidic pH of the organella increases to a greater degree than when two drugs are given separately, and the process saturates more efficiently. These mechanisms may produce an interaction at the level of cellular distribution, which results in a decrease in drug concentrations in lysosomes (depot form) and its increase in cellular membranes and the cytosol. Such interactions have been shown to occur between phenothiazine neuroleptics and antidepressant drugs in tissue slices [11–13] and cell cultures [14]. The above interactions are especially characteristic of psychotropics, e. g. thioridazine and perazine, whose distribution depends to a high extent on lysosomal trapping. The overall results at a body level of such interaction may be a shift of the drugs from organs rich in lysosomes to those poor in these organella (in particular to the heart), as well as an elevation in the free drug concentration [13, 28].

The aim of the present study was to investigate *in vivo* consequences of the distribution interactions between the piperidine-type phenothiazine neuroleptic thioridazine and fluoxetine, which were demonstrated *in vitro* to occur at a level of lysosomal trapping. The results obtained in this study are compared with the findings of analogous interactions between thioridazine and imipramine, and between perazine and fluoxetine, and are discussed with respect to their possible clinical implications.

MATERIALS and METHODS

Drugs and chemicals

Thioridazine (hydrochloride) was obtained from Jelfa (Jelenia Góra, Poland), fluoxetine (hydrochloride) was provided by Eli Lilly (Indianapolis, USA). Mesoridazine and sulforidazine (free bases) were donated by Sandoz Pharma AG (Basel, Switzerland). Thioridazine ring sulfoxide and N-desmethylthioridazine were synthesized in our laboratory as described previously [8]. Acetonitrile, methanol and hexane of the HPLC purity were purchased from E. Merck (Darmstadt, Germany).

Animals

Experiments were carried out on male Wistar rats (240–260 g) kept under standard laboratory conditions. The animals were fed *ad libitum* on standard granulated pellets and had free access to tap water.

In vivo estimation of a distribution interaction between thioridazine and fluoxetine

The rats received thioridazine and fluoxetine separately or jointly, at a dose of 10 mg/kg *ip*. Concentrations of fluoxetine and thioridazine and its metabolites in the plasma and tissues (lungs, liver, kidneys, brain, femural muscles, heart) were measured at 1 h after administration of the drugs (i.e. immediately after the distribution process), according to Daniel and Wójcikowski [13]. Plasma and tissue homogenates (in distilled water) were alkalized (pH 12) and extracted with hexane containing 3% of isoamyl alcohol at pH 12 (30 µl of 3 M NaOH). The drug concentrations were measured using the LaChrom HPLC system (Merck-Hitachi), equipped with a UV detector, an L-7100 pump and a D-7000 System Manager. The analytical column Econosphere C18 (5 µm, 4.6 × 250 mm) was purchased from Alltech (Carnforth, England), and was maintained at an ambient temperature. The mobile phase consisted of an acetate buffer, pH 3.6 (containing 2 ml triethylamine in 1 liter of the buffer) and acetonitrile (42:58 v/v). The flow rate was l.2 ml/min. The absorbance was measured at a wavelength of 270 nm.

Calculations and statistics

Effects of distribution interactions were estimated on the basis of the calculated tissue/plasma and lysosome-poor/lysosome-rich tissue concentration ratios, considering the heart and muscles as

Table 1. The concentration of thioridazine (THIOR) and its metabolites in different tissues at 1 h after administration of THIOR alone (10 mg/kg *ip*) or jointly with fluoxetine (FLX, 10 mg/kg *ip*) to rats. Mean values ± SD are presented (n = 8–10, n = number of animals). The statistical significance was assessed by Student's *t*-test and indicated by * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Tissue/treatment	Concentration of thioridazine and its metabolites					
	Thioridazine	N-desmethyl-thioridazine	Mesoridazine (2-sulfoxide)	Sulforidazine (2-sulfone)	Thioridazine ring sulfoxide (5-sulfoxide)	Thioridazine + metabolites
Plasma [nmol/ml]						
THIOR	0.649 ± 0.198	0.284 ± 0.078	0.395 ± 0.129	0.069 ± 0.017	0.319 ± 0.077	1.716 ± 0.358
THIOR + FLX	1.044 ± 0.426 *	0.183 ± 0.076 *	0.668 ± 0.200 **	0.118 ± 0.031 **	0.508 ± 0.126 **	2.523 ± 0.583 **
Lungs [nmol/g]						
THIOR	8.826 ± 2.349	12.347 ± 2.195	7.036 ± 1.749	1.412 ± 0.255	6.076 ± 1.055	35.697 ± 5.555
THIOR + FLX	7.574 ± 1.218	5.866 ± 1.917 ***	4.685 ± 1.613 **	1.636 ± 0.323	0.757 ± 0.296 ***	20.251 ± 4.685 ***
Liver [nmol/g]						
THIOR	5.699 ± 1.386	4.538 ± 0.965	3.503 ± 0.752	1.400 ± 0.281	1.697 ± 0.378	16.837 ± 1.776
THIOR + FLX	7.039 ± 1.032 *	3.073 ± 0.507 **	2.681 ± 0.651 *	1.426 ± 0.323	2.171 ± 0.642	16.702 ± 2.337
Kidneys [nmol/g]						
THIOR	9.987 ± 2.289	3.620 ± 0.779	1.593 ± 0.288	0.901 ± 0.078	1.992 ± 0.429	18.093 ± 3.157
THIOR + FLX	13.822 ± 3.386 *	3.568 ± 1.381	1.781 ± 0.693	1.641 ± 0.468 ***	3.547 ± 1.170 **	26.685 ± 3.982 *
Brain [nmol/g]						
THIOR	3.827 ± 1.170	0.265 ± 0.078	0.103 ± 0.030	0.148 ± 0.031	0.322 ± 0.058	4.665 ± 1.696
THIOR + FLX	4.276 ± 1.350	0.237 ± 0.102	0.111 ± 0.058	0.109 ± 0.038 *	0.307 ± 0.076	5.120 ± 1.532
Muscles [nmol/g]						
THIOR	1.175 ± 0.122	0.615 ± 0.086	0.354 ± 0.082	0.043 ± 0.008	0.373 ± 0.128	2.560 ± 0.405
THIOR + FLX	2.600 ± 0.199 ***	0.823 ± 0.118 **	0.387 ± 0.131	0.047 ± 0.012	0.477 ± 0.073	4.334 ± 0.415 ***
Heart [nmol/g]						
THIOR	1.182 ± 0.164	1.027 ± 0.333	0.461 ± 0.133	0.401 ± 0.086	0.615 ± 0.144	3.686 ± 0.588
THIOR + FLX	3.910 ± 0.285 ***	3.714 ± 0.240 ***	1.297 ± 0.417 ***	0.252 ± 0.042 **	2.351 ± 0.599 ***	11.524 ± 0.706 ***

lysosome-poor tissues and the lungs, liver and kidneys as lysosome-rich ones. The obtained results were evaluated statistically using Student's *t*-test.

RESULTS

An *in vivo* study carried out at 1 h after *ip* administration of thioridazine and/or fluoxetine to rats (Tab. 1) showed that fluoxetine significantly increased the concentration of thioridazine in plasma (up to 161% of the thioridazine-treated group), liver, kidneys, femural muscles and heart. The highest increases in the neuroleptic concentrations were found in the heart and muscles (up to 331 and 221% of the thioridazine-treated group, respectively). Changes in the concentrations of thioridazine metabolites in the plasma and tissues did not follow closely those of the parent compound. Fluoxetine elevated the concentrations of N-desmethylthioridazine in the muscles and heart and decreased its concentration in the plasma, lungs and liver. Simultaneously, the antidepressant caused an increase in the concentration of mesoridazine in the plasma and heart and its decrease in the lungs and liver. The concentration of sulforidazine rose in the plasma and kidneys, but it declined in the brain and heart. Moreover, fluoxetine increased the concentration of thioridazine 5-sulfoxide in the plasma, kidneys and heart, while its level in the lungs was decreased. The sum of concentrations of thioridazine and its metabolites measured in the plasma, kidneys, muscles and heart were raised by fluoxetine. In contrast, the sum of concentration of thioridazine and its metabolites in the lungs was lowered

Table 2. The concentration of fluoxetine (FLX) in different tissues at 1 h after administration of FLX alone (10 mg/kg *ip*) or jointly with thioridazine (THIOR, 10 mg/kg *ip*) to rats. Mean values ± SD are presented (n = 9–10, n = number of animals). The statistical significance was assessed by Student's *t*-test and indicated by * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Tissue/treatment	Concentration of fluoxetine
Plasma [nmol/ml]	
FLX	0.660 ± 0.170
FLX + THIOR	1.012 ± 0.337 *
Lungs [nmol/g]	
FLX	12.083 ± 5.073
FLX + TIOR	14.278 ± 3.769
Liver [nmol/g]	
FLX	4.081 ± 1.261
FLX + TIOR	5.694 ± 1.279 *
Kidneys [nmol/g]	
FLX	6.421 ± 1.844
FLX + TIOR	9.230 ± 2.560 *
Brain [nmol/g]	
FLX	2.047 ± 0.853
FLX + TIOR	4.020 ± 2.007 *
Muscles [nmol/g]	
FLX	1.870 ± 0.429
FLX + TIOR	2.458 ± 0.449 **
Heart [nmol/g]	
FLX	1.056 ± 0.426
FLX + TIOR	1.996 ± 0.272 ***

Table 3. The tissue/plasma concentration ratios of thioridazine (THIOR) and fluoxetine (FLX) *in vivo* at 1 h after separate or joint administration of the drugs (10 mg/kg *ip*) to rats. Mean values ± SD are presented (n = 8–10, n = number of animals). The statistical significance was assessed by Student's *t*-test and indicated by * $p < 0.05$, ** $p < 0.01$

Drug concentration/ treatment	C_{tissue}/C_{plasma}					
	Lungs	Liver	Kidneys	Brain	Muscles	Heart
Thioridazine						
THIOR	13.599 ± 4.623	8.781 ± 3.118	15.388 ± 3.239	5.897 ± 1.724	1.810 ± 0.733	1.821 ± 0.739
THIOR + FLX	7.723 ± 3.856 *	8.027 ± 2.481	13.329 ± 2.609	4.531 ± 1.154	2.788 ± 1.067 *	4.016 ± 1.286 **
Fluoxetine						
FLX	17.487 ± 7.200	5.858 ± 2.198	9.261 ± 3.196	2.284 ± 0.958	2.781 ± 1.192	1.243 ± 0.544
FLX + THIOR	15.653 ± 7.340	6.003 ± 2.322	10.173 ± 3.927	4.105 ± 1.559 *	2.768 ± 1.147	2.075 ± 0.748 *

Table 4. The lysosome-poor/lysosome rich tissue concentration ratios of thioridazine (THIOR) and fluoxetine (FLX) *in vivo* at 1 h after separate or joint administration of the drugs (10 mg/kg *ip*) to rats. Mean values ± SD are presented (n = 8–10, n = number of animals). The statistical significance was assessed by Student's *t*-test and indicated by * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Drug concentration/ treatment	Lysosome-poor/lysosome rich tissue concentration ratios					
	Heart/lungs	Heart/liver	Heart/kidneys	Muscles/lungs	Muscles/liver	Muscles/kidneys
Thioridazine						
THIOR	0.134 ± 0.040	0.207 ± 0.061	0.118 ± 0.014	0.134 ± 0.026	0.206 ± 0.050	0.118 ± 0.032
THIOR + FLX	0.526 ± 0.129 ***	0.569 ± 0.079 ***	0.263 ± 0.069 ***	0.343 ± 0.06 ***	0.378 ± 0.071 ***	0.180 ± 0.056 *
Fluoxetine						
FLX	0.087 ± 0.053	0.279 ± 0.123	0.171 ± 0.086	0.180 ± 0.096	0.535 ± 0.129	0.298 ± 0.105
FLX + THIOR	0.158 ± 0.031 **	0.351 ± 0.078	0.243 ± 0.099	0.187 ± 0.077	0.456 ± 0.146	0.279 ± 0.073

by the antidepressant. At the same time, thioridazine increased fluoxetine concentrations in both plasma (up to 153% of the fluoxetine-treated group) and all the investigated tissues except for the lungs (Tab. 2). The highest increases in fluoxetine concentration were found in the brain and heart (up to 196 and 189% of the fluoxetine-treated group, respectively).

Fluoxetine diminished the calculated tissue/plasma concentration ratio of thioridazine for the lungs, but elevated those ratios for the muscles and heart (Tab. 3). The antidepressant did not change the liver/plasma, kidneys/plasma and brain/plasma concentration ratios of thioridazine. On the other hand, thioridazine elevated the brain/plasma and heart/plasma concentration ratios of fluoxetine. However, thioridazine did not affect the lungs/plasma, liver/plasma, kidneys/plasma and muscles/plasma concentration ratios of fluoxetine.

Consequently, the thioridazine lysosome-poor/lysosome-rich tissue concentration ratios significantly increased in the presence of fluoxetine (Tab. 4). At the same time thioridazine raised (or had such a tendency) the heart/lysosome-rich tissue concentration ratios of fluoxetine, not changing significantly the muscles/lysosome-rich tissue concentration ratios of the antidepressant.

DISCUSSION

Our previous *in vitro* studies showed that interactions between phenothiazine neuroleptics and antidepressants could occur at a level of lysosomal trapping. This kind of interactions leads to a decrease in the intralysosomal (depot) drug concentration and, consequently, to an elevation in the membrane and free drug concentrations, i.e. concentrations relevant to pharmacological action [11–13]. Therefore, it was hypothesized that *in vivo* the above interactions can result in a shift of a lipophilic drug from organs abundant in lysosomes (the lungs, kidneys, liver) to those poor in these organella (the heart, muscles). The hypothesis has recently been supported by the complementary studies of the distribution interaction between perazine and antidepressants (imipramine, fluoxetine) [28], as well as between thioridazine and imipramine [13] *in vitro* and *in vivo*.

The presented results provide further evidence reinforcing the above hypothesis by showing that the distribution interactions between thioridazine and fluoxetine observed *in vitro* occur also *in vivo*, leading to a shift of the drugs from organs rich in lysosomes to those poor in these organella, in particular to the heart. Thus, the investigated drugs mutually increased their heart/plasma and heart/lysosome-rich tissue concentration ratios, i.e. the heart/lung, heart/liver and heart/kidneys ratios. Similar results were obtained with lysosome-poor muscles in the case of thioridazine.

The obtained results show that, like *in vitro*, *in vivo* thioridazine and fluoxetine accumulated to a considerable degree in tissues abundant in lysosomes (mainly in the lungs), and the influence of the antidepressant on the distribution of thioridazine was somewhat stronger than that of neuroleptic on the distribution of antidepressant, which may result from different lysosomotropic properties and rates of penetration of the drugs [10, 13]. However, in many cases we did not observe the expected

changes in the tissue/plasma concentration ratios (i.e. a decrease for tissues abundant and an increase for tissues poor in lysosomes) or lysosome-poor/lysosome-rich tissue concentration ratios (i.e. an increase).

In the case of tissues containing cytochrome P-450 isoenzymes responsible for drug metabolism (mainly the liver, but also the lungs and kidneys), a lack of an appropriate change in the tissue/plasma concentration ratio may result from metabolic interaction (an increase in the drug concentration), which may mask an interaction at the level of lysosomal trapping (a decrease in the drug concentration). On the other hand, a stronger effect of the distribution interaction in the heart than in the muscles may also result from physiological conditions. Although both the heart and femural muscles belong to tissues not abundant in lysosomes, the muscles contain 1.5–2 times more of these organella [5, 20]. Thus, a local effect of the distribution interaction at the level of lysosomal trapping (a decrease in drug concentration) is bigger in the muscles than in the heart, and may, therefore, compensate for a shift of the drug from organs rich in lysosomes to the muscles (an increase in the drug concentration). Moreover, after the distribution interaction in the organs rich in lysosomes, the drug is transported by blood first to the heart and then to other tissues. Consequently, a drug leaving the lysosome-rich organs passes through the heart when its blood concentration is the highest, being taken up by the well perfused organ.

Thioridazine did not affect the muscle/plasma and the muscles/lysosomal-rich tissue concentration ratios of fluoxetine. These results differ from our recent data which showed that thioridazine increased the muscle/plasma and the muscles/lysosomal-rich tissue concentration ratios of imipramine [13]. The observed differencies in the effects of thioridazine on the distribution of the antidepressants may be due to a somewhat greater contribution of the phospholipid binding than lysosomal trapping to the total uptake of fluoxetine by lysosome-rich tissues, and, to a lower total uptake of fluoxetine by the muscles, compared to imipramine [10]. The consequence of the above differences may be a shift of a smaller pool of fluoxetine than imipramine from the lysosome-rich tissues to the muscles, and a lesser ability of muscles to bind fluoxetine. On the other hand, the difference between the presented here thioridazine-fluoxetine interaction and the previously investigated perazine-fluoxetine interaction lies in the lack of an increase in the muscle/liver ratio for perazine as a result of extremely strong inhibition of perazine metabolism by fluoxetine, leading to the 2.5-fold increase in perazine concentration in the liver [28].

As a result of interactions between thioridazine and fluoxetine, the brain/plasma concentration ratio of fluoxetine increased, indicating that the organ behaved like tissues not abundant in lysosomes. This remains in agreement with the distribution pattern of the highly lysosomotropic drug chloroquine suggesting relatively low density of lysosomes in the brain [5]. However, fluoxetine had a tendency to diminishing the brain/plasma ratio of thioridazine, though it increased that ratio for perazine [28]. The pharmacokinetics of thioridazine differs from that of other phenothiazine neuroleptics. Its brain/plasma concentration ratio is considerably lower [8, 26], which implies a relatively smaller contribution of phospholipid binding (with a relatively higher contribution of lysosomal trapping) to the brain uptake of this drug. These findings were confirmed by our *in vitro* studies which showed that among the studied psychotropics thioridazine showed the highest degree of lysosomotropism in the brain [10, 13]. Thus, in the case of thioridazine, the brain may behave like a tissue abundant in lysosomes. Such a phenomenon was also observed in our earlier *in vivo* studies concerning thioridazine-imipramine interaction [13].

The distribution interaction observed *in vivo* may also involve drug metabolites that are basic lipophilic compounds. Since the metabolites of the psychotropics are biologically active (e.g. mesoridazine, sulforidazine, N-desmethylthioridazine, N-desmethylfluoxetine) and can have an impact on potential pharmacological response and adverse effects, concentrations of both the parent compounds and their metabolites should be considered.

In conclusion, the present results show that the distribution interactions between thioridazine and fluoxetine found *in vitro*, also take place *in vivo*, leading to the shift of the drugs from organs rich in lysosomes to those poor in the organella, mainly to the heart. Apart from lysosome density in the investigated tissues, the potential metabolic interactions in the liver and the pattern of drug circulation in the body have an important impact on tissue concentrations and on the calculated drug concentration ratios. The observed interactions may be of

clinical importance, since thioridazine may be combined with SSRIs in the treatment of complex or "treatment-resistant" psychiatric disorders. Clinical consequences of such interactions may involve potentiation of the pharmacological action of the co-administered drugs in the brain and an increased risk of cardiotoxic and anticholinergic side-effects of thioridazine as a result of intracellular and inter-tissue shifts of the drugs. Modifications of dosages of such drugs require particular caution, since monitoring plasma levels does not reflect fully the changes in tissue drug concentrations (e.g. in the brain and heart) produced by distribution interactions.

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