

The Effects of Tamoxifen and Estrogen on Brain Metabolism in Elderly Women

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Background: Tamoxifen is used to treat breast cancer and may reduce the risk of breast cancer. However, there are conflicting reports as to whether tamoxifen use is associated with changes in brain metabolism and function or cognitive impairment. Consequently, we assessed the effects of tamoxifen and estrogen on the brain chemistry of elderly women. **Methods:** We used proton magnetic resonance spectroscopy to measure the concentrations of *N*-acetyl-containing compounds, *myo*-inositol (MI), total creatine (creatine plus phosphocreatine), and choline-containing compounds in the frontal white matter, basal ganglia, and hippocampus of 76 elderly women of whom 16 had received tamoxifen therapy, 27 had received estrogen as hormone replacement therapy (HRT), and 33 had received neither (control group). A two-way analysis of variance (ANOVA) was performed to determine the statistical significance of differences in cerebral metabolite concentrations among subject groups and brain regions. All statistical tests were two-sided. **Results:** Women in the tamoxifen and HRT groups had lower concentrations of MI in all areas than women in the control group ($P = .02$; overall group effect on ANOVA). Compared with the control group, the tamoxifen group ($P = .004$) and the HRT group ($P = .06$) had lower concentrations of MI in their basal ganglia. The MI concentration in the basal ganglia was inversely correlated with the duration of tamoxifen treatment ($\rho = -.72$; $P = .005$). **Conclusions:** The reduced concentrations of MI in the brains of women treated with tamoxifen and HRT, compared with those of control women, suggest that tamoxifen has an effect similar to that of estrogen. These results, if confirmed, may alleviate concerns about the safety of using tamoxifen to reduce breast cancer risk in elderly women. [J Natl Cancer Inst 2002;94:592-7]

Tamoxifen is an estrogen receptor agonist and antagonist that is widely used to treat breast cancer (1). Recent results suggest that tamoxifen also reduces the risk of developing breast cancer (2,3) and may be offered for this indication after the long-term risks and benefits are considered (4-7). Two studies (8,9) have demonstrated that estrogen has positive effects on brain metabolism and function. However, a preclinical study (10) has suggested that tamoxifen may also act as an estrogen antagonist in the brain. In addition, the combined use of tamoxifen and chemotherapy in the clinic has been associated with cognitive impairment (11). Such results have led to the hypothesis that tamoxifen may negatively affect brain metabolism, especially in elderly women.

We used proton magnetic resonance spectroscopy (^1H MRS), a neuroimaging technique that can measure the concentrations of biochemical markers associated with brain injury, to perform a cross-sectional study to compare brain metabolism in women with breast cancer who had received tamoxifen with that in healthy women who had received hormone replacement therapy

(HRT) without tamoxifen and with that in healthy women who had not received either tamoxifen or HRT. We determined the concentrations of four metabolites: *N*-acetyl-containing compounds (NA), including *N*-acetyl-L-aspartate, a neuronal marker that reflects neuronal density and integrity (12); *myo*-inositol (MI), a putative glial marker whose levels reflect glial content or activity (13); total creatine (CR), which reflects high-energy phosphate metabolism (14); and choline-containing compounds (CHO) associated with cell membrane metabolism (15). Numerous MRS studies [e.g., (16,17)] in patients with various neurologic disorders have suggested an association between increased cerebral MI and glial proliferation in response to brain injury. Therefore, we hypothesized that an estrogen-antagonistic effect of tamoxifen might be associated with increased cerebral MI concentrations, indicating brain injury.

SUBJECTS AND METHODS

Study Subjects

Three groups of age-matched women (total $n = 76$) between the ages of 65 and 80 years were recruited from the local community, a suburban area in the southwestern part of Los Angeles County, through advertisements, and from solicitations through the mail. Recruitment in all three subject groups occurred in parallel, and women fulfilling the study criteria were enrolled immediately. Verbal and written informed consent were obtained from each woman, according to procedures approved by the Institutional Review Board of the Harbor-UCLA Research and Education Institute (REI) and in accordance with an assurance filed with and approved by the U.S. Department of Health and Human Services. The tamoxifen group ($n = 16$) included women who were diagnosed with localized breast cancer, had undergone resection, and had received tamoxifen (20 mg/day) for at least 2 years (range = 2-10 years; mean \pm standard deviation (SD) = 4.4 ± 1.7 years) but had never received any systemic chemotherapy or estrogen as HRT. The HRT group ($n = 27$) consisted of healthy women with no history of breast cancer who had received HRT for at least 2 years (range = 2-55 years; mean \pm SD = 20.8 ± 10.5 years). HRT consisted of oral conjugated equine estrogen (Premarin; Wyeth, Madison, NJ) at 0.625 mg/day [$n = 25$]; Premarin at 1.25 mg/day [$n = 1$]; and estropipate at 0.75 mg/day [$n = 1$]; in addition, three women

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who received Premarin at 0.625 mg/day also received intermittent medroxyprogesterone (Provera; Pharmacia Upjohn Co., Kalamazoo, MI) at 10 mg/day. The control group ($n = 33$) consisted of healthy women with no history of breast cancer who were never treated with tamoxifen, chemotherapy, or HRT. All study subjects were evaluated by a physician at the General Clinical Research Center at Harbor-UCLA REI to ensure that they did not have recurrent breast cancer, psychiatric disorders, chronic medical or neurologic illnesses (e.g., uncontrolled hypertension, abnormal thyroid function, diabetes, strokes, Alzheimer's disease, or Parkinson's disease) that might affect cognition, a history of head trauma with loss of consciousness for more than 1 hour, or any contraindication for the imaging studies, any of which would have excluded them from our study. Clinical evaluations of the study subjects included a medical history, physical and neurologic examination, blood pressure assessments, an electrocardiogram, a battery of comprehensive screening blood tests (complete blood count, chemistry panel, thyroid function tests, and quantitation of rapid plasma reagin, vitamin B₁₂, and folate levels), and urinalysis. Each subject also completed a standardized cognitive screening form [modified Mini-Mental State Examination (18)] and two neuropsychologic tests, the Digit Symbol Substitution Test and the Trail Making Test-part A (19), which evaluated psychomotor speed.

Imaging Studies

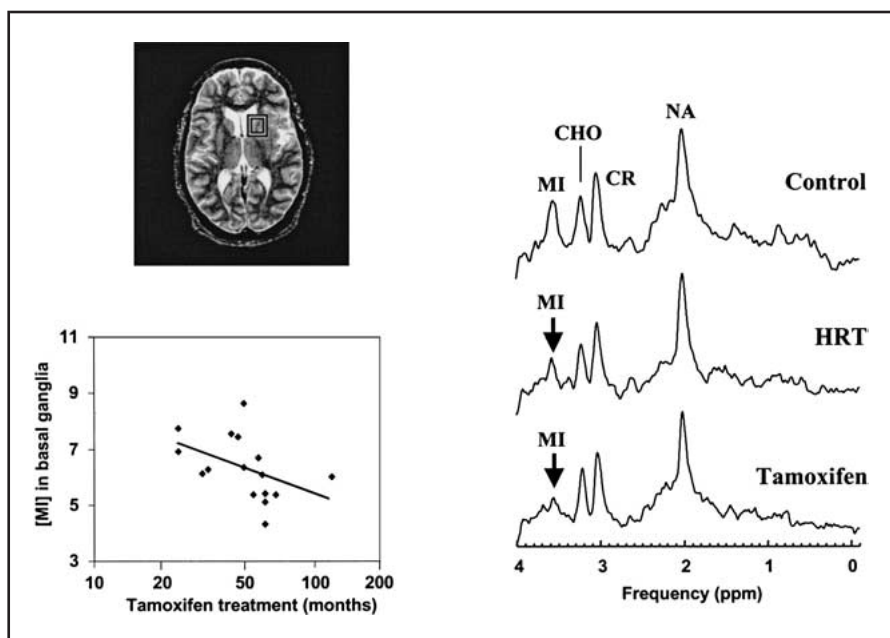
Magnetic resonance imaging (MRI) scans were performed on a 1.5-Tesla scanner (General Electric Medical Systems, Milwaukee, WI). After obtaining a sagittal T1-weighted localizer (echo time [TE]/relaxation time [TR] = 11/500 ms, 5-mm thickness, 1-mm gap), we performed an axial fast spin echo sequence (TE1/TE2/TR = 17/102/4000 ms, 5-mm thickness, no gap) and an axial fluid-attenuated inversion recovery sequence (TE/inversion time [TI]/TR = 142/2600/11000 ms) on each study subject. We then performed localized ¹H MRS in each of three volumes of interest in the brain: the frontal white matter, the basal ganglia, and the left hippocampal region. The volumes of interest ranged between 3 and 5 cm³. We were very careful to ensure that each volume of interest included the same anatomic structures across

subjects. The volume of interest in the basal ganglia contained mostly deep gray matter (putamen, globus pallidus, and a portion of the head of the caudate) and a small portion of the white matter (internal capsule) (Fig. 1). MRS data for each volume of interest were acquired using a double spin echo sequence, which was optimized for the acquisition of ¹H MR spectra from the frontal lobe (20,21). The acquisition parameters for all volumes of interest were TE/TR = 30/3000 ms, and 64 traces were averaged. We determined the cerebral concentrations of NA, MI, CR, and CHO, corrected for the presence of cerebrospinal fluid in each voxel, as previously described (22). Typical intrasubject variabilities in the concentrations of NA, CR, CHO, and MI were less than 10% (23).

Statistical Analyses

Statistical analyses were performed in StatView version 5.0 (SAS Institute, Cary, NC). A mixed two-way analysis of variance (ANOVA) was performed to determine the statistical significance of differences in cerebral metabolite concentrations among the three brain regions (within-variable; random effect) and among the three subject groups (between-variable; fixed effect). Kolmogorov-Smirnov tests demonstrated that the cerebral metabolite concentrations were normally distributed. A type I error probability of $P \leq .05$ was used to determine statistical significance for main effects on the ANOVA. For variables that showed statistical significance on ANOVA, Student's *t* tests were performed to determine the statistical significance of differences between individual groups for each brain region. Because nine of these *t* tests were performed for each variable (three groups times three brain regions), only differences with a probability $P < .0055$ ($= .05/9$) were considered statistically significant for the *post hoc* tests. Spearman correlations were performed to test for possible relationships between metabolite concentrations and the duration of treatment with tamoxifen or estrogen. A probability of $P \leq .05$ was used to determine statistical significance for these correlation analyses. All statistical tests were two-sided.

Fig. 1. Representative proton magnetic resonance spectra from the basal ganglia region of a subject from each of the three treatment groups (right). The area under each peak was used to determine metabolite concentrations. The concentration of *myo*-inositol (MI) was lower in the woman who received hormone replacement therapy (HRT) or tamoxifen than in the woman who received neither (Control). The voxel location in the basal ganglia is indicated in the axial magnetic resonance imaging (MRI) (top left). The graph (bottom left) shows the dependence of the MI concentration (in mmol/kg) in the basal ganglia on the duration of tamoxifen treatment (logarithmic scale). NA = *N*-acetyl resonance; CR = total creatine (creatine plus phosphocreatine) resonance; CHO = resonance of choline-containing compounds; ppm = parts per million.



RESULTS

The ages of the women in the three groups were tightly matched and not statistically significantly different among the groups ($P = .52$). The mean (\pm SD) ages were 71.8 (\pm 4.1) years for the control group, 71.5 (\pm 4.1) years for the HRT group, and 70.4 (\pm 4.7) years for the tamoxifen group. There was no statistically significant difference in the average number of years of education among the three groups (control group = 14.1 years; HRT group = 14.8 years; tamoxifen group = 13.2 years; $P = .15$). We detected no cognitive deficits in any of the women or intergroup differences in cognition; for example, on a scale of 0–100 for cognitive assessment (with 100 being the highest cognitive score), women in the tamoxifen, HRT, and control groups had mean (\pm SD) cognitive scores of 95.9 (\pm 3.5), 95.4 (\pm 4.5), and 95.2 (\pm 4.9), respectively. The only finding upon neurologic examination was mild essential tremor in 19 women (six women [22%] in the HRT group, five women [31%] in the tamoxifen group, and eight women [24%] in the control group). The results of two neuropsychologic tests that are sensitive to psychomotor speed and that can detect motor disorders in the upper extremities were not statistically significantly different among the three groups. For example, in the Digit Symbol Substitution Test, the number of correct substitutions after 90 seconds (\pm SD) for women in the HRT, tamoxifen, and control groups were 7.0 ± 1.7 , 7.5 ± 3.1 , and 7.2 ± 2.1 substitutions, respectively ($P = .91$), whereas in the Trail Making Test-part A, the time (\pm SD) required to connect 20 consecutively numbered circles was 38.8 ± 13.8 seconds for women in the HRT group, 44.2 ± 12.2 seconds for women in the tamoxifen group, and 36.9 ± 10.4 seconds for women in the control group ($P = .27$). Structural MRI scans showed no major structural abnormalities (i.e., cortical infarcts, tumors, or vascular malformations) in any study subject. However, nearly half of all the women (49%) had small or moderate white matter hyperintensities in the periventricular regions; no intergroup differences were observed with respect to these lesions. We also observed possible silent lacunar infarcts (small lesions showing hyperintensity on T2-weighted MRI and hypointensity on T1-weighted images) in three women in the HRT group but not in any women in the other two groups.

The ANOVA demonstrated a statistically significant difference in the MI concentrations among the three treatment groups ($P = .02$; group effect on ANOVA) and among the three brain regions ($P < .001$; brain region effect on ANOVA). However, MI concentration did not differ statistically significantly among the three brain regions by treatment group ($P = .50$; interaction between treatment group status and brain region). The overall concentration of MI was statistically significantly lower in the tamoxifen ($P = .01$) and HRT ($P = .03$) groups than in the control group. The difference in the MI concentration among the treatment groups was most pronounced in the basal ganglia. For example, the MI concentration in the basal ganglia was statistically significantly lower in the tamoxifen group (6.33 mmol/kg) than it was in the control group (7.57 mmol/kg) ($P = .004$; difference in MI concentration between the tamoxifen group and the control group = -1.24 mmol/kg [95% confidence interval {CI} = -0.43 to -2.05 mmol/kg]; Table 1). The MI concentration was also lower in the basal ganglia of the HRT group (6.73 mmol/kg) than it was in the control group (7.57 mmol/kg), but that difference was not statistically significant ($P = .06$; difference in MI concentration between HRT group and control group = -0.83 mmol/kg [95% CI = -1.71 to 0.05 mmol/kg]). There was an inverse relationship between the duration of tamoxifen treatment and the MI concentrations in the basal ganglia ($\rho = -.72$; $P = .005$) and in the hippocampus ($\rho = -.50$; $P = .04$) (Fig. 1). There were no statistically significant effects of group status or differential group effects in the three brain regions for the other three metabolites measured in this study.

DISCUSSION

Our initial hypothesis, that tamoxifen would increase MI concentrations in the brain, proved incorrect. Instead, we found that women who took tamoxifen or HRT had statistically significantly lower levels of MI in their brains than did women who received no drug therapy. Because normal aging is associated with increases in the cerebral concentrations of MI (24), the reduced MI concentrations that we observed in women who received tamoxifen or HRT suggest that both of these therapies may be associated with the favorable modulation of brain aging.

Table 1. Cerebral metabolite concentrations (mmol/kg)*

Region of the brain/group	Metabolite, mmol/kg			
	NA (95% CI)	CR (95% CI)	CHO (95% CI)	MI (95% CI)†
Basal ganglia				
Tamoxifen	8.51 (8.13 to 8.89)	8.92 (8.30 to 9.54)	2.06 (1.91 to 2.21)	6.33 (5.73 to 6.93)‡
Control	8.66 (8.30 to 9.02)	8.92 (8.54 to 9.30)	2.14 (2.01 to 2.27)	7.57 (6.99 to 8.15)
HRT	8.75 (8.43 to 9.07)	8.97 (8.57 to 9.37)	2.13 (1.98 to 2.28)	6.73 (6.03 to 7.43)
Frontal white matter				
Tamoxifen	7.39 (7.03 to 7.75)	6.69 (6.26 to 7.12)	1.69 (1.58 to 1.80)	7.51 (6.87 to 8.15)
Control	7.42 (7.14 to 7.70)	6.52 (6.22 to 6.82)	1.76 (1.65 to 1.87)	7.57 (7.17 to 7.97)
HRT	7.49 (7.19 to 7.79)	6.37 (6.09 to 6.65)	1.67 (1.54 to 1.80)	7.28 (6.81 to 7.75)
Hippocampus				
Tamoxifen	9.04 (8.53 to 9.55)	8.66 (8.08 to 9.24)	2.80 (2.61 to 2.99)	10.10 (9.42 to 10.78)
Control	8.62 (8.26 to 8.98)	8.32 (7.94 to 8.70)	2.79 (2.64 to 2.94)	10.60 (10.09 to 11.11)
HRT	8.69 (8.24 to 9.14)	8.51 (8.11 to 8.91)	2.74 (2.57 to 2.91)	9.82 (9.29 to 10.35)

*CI = confidence interval; NA = *N*-acetyl-containing compounds; CR = total creatine; CHO = choline-containing compounds; MI = *myo*-inositol; HRT = hormone replacement therapy.

† $P = .02$ (group effect on analysis of variance).

‡Statistically significantly lower ($P \leq .004$); *t* test, uncorrected for multiple comparisons) than the MI concentration in the basal ganglia of control subjects ($P < .04$ after correction for multiple [$n = 9$] comparisons).

The inverse relationship between the MI concentration in the basal ganglia and the length of tamoxifen treatment suggests that longer exposures to tamoxifen may be more beneficial to brain metabolism than short exposures; however, this issue should be addressed more thoroughly in a longitudinal study. The lack of a relationship between the duration of HRT and cerebral metabolite concentrations, however, could suggest that the effects of HRT on brain chemistry may reach a steady state much earlier than 20 years, the average duration of HRT for women in this study.

Results of several recent reports are consistent with our findings and support our conclusion that both tamoxifen and estrogen may have similar effects in the brain. Several preclinical studies (25,26) have suggested that estrogen could be neuroprotective, possibly by blocking oxidative stress-induced neuronal death (27). Another study (28) found that both estrogen and tamoxifen protect glial cells from glutamate-mediated cytotoxicity and stimulate cell differentiation. Furthermore, induction of the expression of aromatase, the enzyme that produces estrogen *de novo* in astrocytes, is thought to be part of the glial repair response to brain injury (29), and estrogen receptors are expressed in reactive astrocytes in response to injury in the primate brain (30). Finally, both estrogen and tamoxifen increased synaptic density in ovariectomized rats (31). These findings all support a neuroprotective or repair role for estrogen and tamoxifen. Alternatively, based on the observation that glial activity increases with normal brain aging in mice (32), it is possible that the women who received estrogen or tamoxifen had lower concentrations of the glial marker MI in their brains because of a slowing of the aging process in their brains.

Clinical studies provide additional support for our conclusion that estrogen and tamoxifen do not cause brain injury and/or may be neuroprotective. One prospective breast cancer trial (33) separated the effects of tamoxifen and chemotherapy on cognition and found no influence of tamoxifen on patients' self-reports of cognitive function. A large-scale, retrospective cross-sectional study (34) that used the New York State Medical Data System (NYS-MDS) to evaluate 6925 female nursing home residents over 65 years of age found that, compared with women who had never taken tamoxifen, women who took tamoxifen were less likely to have a diagnosis of Alzheimer's disease, were statistically significantly ($P < .01$) more independent in performing activities of daily living, and had better cognitive skills for daily decision making. Two other studies found no such positive effect of tamoxifen on mental health (35) or cognition (36) among relatively younger women. The first of these studies, from the health-related quality-of-life component of the National Surgical Adjuvant Breast and Bowel Project Prevention Trial, reported baseline and 36-month data for 11 064 women, with an average age of 58 years, that were obtained from two screening questionnaires [Center for Epidemiological Studies-Depression Scale and the Medical Outcomes Study 36-Item Short Form Health Status Survey (35)]. That study found that women treated with tamoxifen had similar depressive symptoms, quality of life, and mental health as did women treated with placebo. By contrast, elderly nursing home residents in the NYS-MDS study who received tamoxifen were 42% more likely to have had a diagnosis of depression than were those who did not receive tamoxifen. In the second study that failed to show a positive effect of tamoxifen on cognition, follow-up questionnaires designed to assess cognitive function (e.g., testing the ability to

draw a clock, copy a box, and write a narrative describing a picture) were mailed to 1163 breast cancer patients whose ages ranged from 57 to 75 years. That study (36) found that cognitive function in women who had used tamoxifen for the standard term (4–5 years) was not statistically significantly lower than that in women who had not used tamoxifen, although the women who were current users of tamoxifen complained more about memory problems than the nonusers of tamoxifen. However, these studies had several potential confounding variables, such as the diagnosis of cancer or other chronic medical illnesses, as possible causes for increased depression (30) and the higher frequency of follow-up visits to doctors by current users of tamoxifen than by nonusers (31), which might have accounted for the higher number of memory complaints in the former group. These confounding variables need to be controlled for in future prospective studies.

Taken together, the findings from these published studies are consistent with the normal cognitive screening assessments that we observed for women on tamoxifen in our study. However, these large surveys and our screening assessments of cognition used relatively simple tests of cognitive function, each with recognized sensitivity limitations; therefore, more detailed neuropsychologic tests are necessary to determine whether tamoxifen use is merely nonharmful or whether it has beneficial effects on cognitive function. Future studies should also evaluate the interaction between age and the effects of tamoxifen. Because both studies that found positive effects of tamoxifen on the brain (the NYS-MDS study and our study) included only women aged 65 years or older, it is possible that the apparent neuroprotective effects of tamoxifen are more evident in older patients who might have some decline in cognitive abilities as a result of normal aging.

In contrast to the cognitive assessment surveys, in which responses and/or performance might be confounded by many factors such as effort or depression, our measurements of brain metabolite concentrations by MRS may provide a more objective way to evaluate the integrity of neuronal and glial function. We found no difference in the concentration of NA, which includes the neuronal marker *N*-acetyl-L-aspartate, between women who received tamoxifen and those who received either HRT or no drug therapy. This result suggests that tamoxifen use is not associated with substantial neuronal injury or loss. In addition, the similar levels of MI in the brains of women who used tamoxifen and those who used estrogen suggest that tamoxifen does not have a negative, antiestrogenic effect on the brain.

Several potential study limitations might affect the interpretation of our findings. First, because of the cross-sectional, non-randomized design of our study, factors other than drug treatment status might have affected the outcome. For example, differences in brain metabolism among the study groups may be related to vascular abnormalities or motor disorders in these elderly women. However, this possibility is unlikely because we excluded all women with a clinical history of stroke, cortical infarcts on MRI, uncontrolled hypertension, diabetes, or any neuropsychiatric disorders from our study. Furthermore, we conducted two neuropsychologic tests that would have identified those subjects with signs similar to those found in Parkinson's disease (37) and found no differences in test results between the women treated with HRT and those treated with tamoxifen or with no drugs at all. A second limitation of our study concerns

potential differences among the study groups in the amounts of gray and white matter in the MRS volumes of interest, especially in the basal ganglia, which contains mostly deep gray matter with some admixture of white matter. However, a detailed analysis of the measured metabolite concentrations in the various brain regions argues against this possibility. In the control group, the MI concentrations in the basal ganglia and in the white matter were essentially identical, whereas the concentrations of CR and CHO were substantially higher in the basal ganglia than in the white matter. Therefore, a change in the gray/white matter composition of the basal ganglia volume in the tamoxifen or HRT groups relative to the control group would not substantially change the MI concentration but would have a marked effect on the CR and CHO concentrations. The fact that we observed the opposite result—a statistically significant change in MI concentration but not in CR and CHO concentrations—argues that there were no substantial differences in the voxel compositions among the three study groups.

In conclusion, the decreased concentration of the glial marker MI in women taking either tamoxifen or estrogen suggests that both drugs may be neuroprotective and may have favorable modulatory effects on aging. The fact that we detected no evidence of neurotoxicity by ¹H MRS, coupled with the accumulating evidence that tamoxifen is either not neurotoxic or even beneficial for cognitive function, further reduces concerns about prescribing tamoxifen to reduce the risk of breast cancer. Future prospective, longitudinal studies involving MRS and detailed neuropsychologic testing of women taking tamoxifen as well as other selective estrogen receptor modulators and aromatase inhibitors that are under evaluation for breast cancer risk reduction are needed to document the long-term effects of such therapies on cognitive function.

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NOTES

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