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The Selective Serotonin Reuptake Inhibitor Fluoxetine Reduces Sexual Motivation in Male Rats

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VEGA MATUSZCZYK, J., K. LARSSON AND E. ERIKSSON. *The selective serotonin reuptake inhibitor fluoxetine reduces sexual motivation in male rats*. PHARMACOL BIOCHEM BEHAV **60**(2) 527–532, 1998.—A male rat put in an open-field arena in which it is free to spend time in the vicinity of—but not in contact with—an estrous female, or in the vicinity of a male, usually spends more time with the female than with the male or elsewhere. Tentatively, the percentage of time spent in the vicinity of the female in this paradigm may be regarded as a measure of sexual motivation. In humans, treatment with selective serotonin reuptake inhibitors (SSRIs) may cause reduced libido. To investigate to what extent serotonin reuptake inhibition influences sexual motivation also in rats, we have tested the effect of subchronic treatment with fluoxetine on the behavior in the sexual motivation test described above; in addition, the effect of fluoxetine on male copulatory behavior was studied. Fluoxetine significantly reduced sexual motivation at subchronic but not at acute administration; moreover, fluoxetine-treated rats displayed an increased ejaculation latency. It is concluded that humans and rats respond similarly to the SSRI fluoxetine with respect to various aspects of sexual behavior. © 1998 Elsevier Science Inc.

Sexual behavior Sexual motivation Serotonin Serotonin reuptake inhibitor Fluoxetine Rats

THE selective serotonin reuptake inhibitors (SSRIs) have become the most frequently prescribed drugs for the treatment of depression. According to early reports the frequency of sexual side effects in patients medicating with SSRIs is less than 2% [see (29)]; however, subsequent studies—in which sexual function has been actively inquired—have shown that sexual dysfunction in patients on SSRIs is considerably more frequent (8). In women, serotonin reuptake inhibitors may cause both anorgasmia and a reduction in libido (9,13,19, 28,32,41); in men, reduced libido and delayed ejaculation are the most common complaints (8,13,20,29). The effect of SSRIs on ejaculation latency has also been used for therapeutic purposes in patients with ejaculatio præcox (5,16,18,22,25,26, 31,36).

When SSRIs are used for the treatment of the acute phase of a depression, the sexual side effects seldom constitute a clinical problem because the disorder per se usually leads to a reduction in sexual interest. However, when used for prophylactic purposes in patients who have recovered from depression, as well as when used for psychiatric conditions that are not associated with a reduction in libido [such as panic disorder, obsessive compulsive disorder, and premenstrual syndrome; for reference, see (12)], the sexual dysfunction induced by these drugs is a problem of considerable clinical significance.

Given the fact that all strong serotonin reuptake inhibitors appear to induce similar sexual side effects, it seems reasonable to assume that these effects are indeed causally related to inhibition of the serotonin transporter and to a subsequent increase in the synaptic concentrations of serotonin. However, neither the postsynaptic receptor subtypes mediating the effects of SSRIs on sexual behavior, nor the brain region in which the effect is exerted, is known. Also, to what extent the reduction in libido and difficulty in achieving orgasm are causally related remains to be clarified.

To enable further characterization of the mechanisms underlying SSRI-induced sexual side effects, an animal model reflecting these effects is warranted. Although there is considerable literature suggesting that serotonin may influence sexual behavior in rodents (for references, see Discussion), stud-

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ies designed to investigate whether the sexual side effects of serotonin reuptake inhibitors observed in humans occur also in rats are sparse (2,35,39,40). To investigate to what extent animal experiments may be used to further analyze the effects of SSRIs on sexual motivation, we investigated the effect of acute and subchronic treatment with the SSRI fluoxetine (15) on the percentage of time a male rat elects to spend in the vicinity of an estrous female [cf. (27)] and on male copulatory behavior.

METHOD

Animals

Wistar rats (Mol:Wist; 60 days of age) were bought from Möllegaard Breeding Laboratories (Vejle, Denmark) and allowed an adaptation period of 2 weeks before the beginning of the experiments. The animals were maintained in groups of same sex, five per cage (Macrolon cage No. 4), under reversed light/dark conditions (lights on between 2200–1000 h) and with controlled temperature (22°C) and humidity conditions (50–60%). Food and tap water were available ad libitum. The experiments were always started two hours after the onset of darkness.

Before the experiments were started, the animals were repeatedly tested for sexual activity. Only those animals that were sexually active were included in the study.

All experiments were approved by the local ethical committee.

Behavior Test Procedures

Sexual motivation test. Sexual motivation was assessed by studying the behavior of a male rat that is allowed to stay in the vicinity of an estrous female or in the vicinity of a sexually active male or elsewhere. The testing apparatus consists of an open-field arena (Plexiglas, 100 × 50 cm) with two plastic boxes (25 × 15 cm) positioned on opposite sides of the arena; in these boxes, the stimuli (i.e., the sexually active male and female) are placed. The positions of the stimuli are changed randomly for each test. The partition between the stimuli and the experimental animal consists of a metal net allowing the animals to see, hear, and smell each other. Platforms (18 × 11 cm) in front of the stimulus compartments are balanced upon microswitches, which are sensed by the controller to record the visits and the duration of each visit to each of the two stimuli.

Testing was performed in a dark, silent room. Each experimental animal was placed in the arena, allowed to adapt for 5 min in the presence of the stimuli and, thereafter, tested for 15 min. After each test, the arena was cleaned with soapy water before another animal was introduced. Percentage of total time spent near the stimulus male, near the stimulus female, and away from both stimuli were registered.

Masculine Sexual Behavior

Ovariectomized female rats brought into estrous by treatment with estradiol benzoate (12.5 μg/rat in sesame oil, SC, −48 h), followed by progesterone (1.0 mg/rat in sesame oil, SC, −6 h) were used as stimuli. The experimental animals were allowed to adapt to the test arena (50 cm in diameter) for 5 min; thereafter, the estrous female was dropped into the arena. The following components of the masculine sexual behavior were recorded: number of mounts without penile intromission, number of mounts with penile intromission, time from the first intromission until ejaculation (ejaculation la-

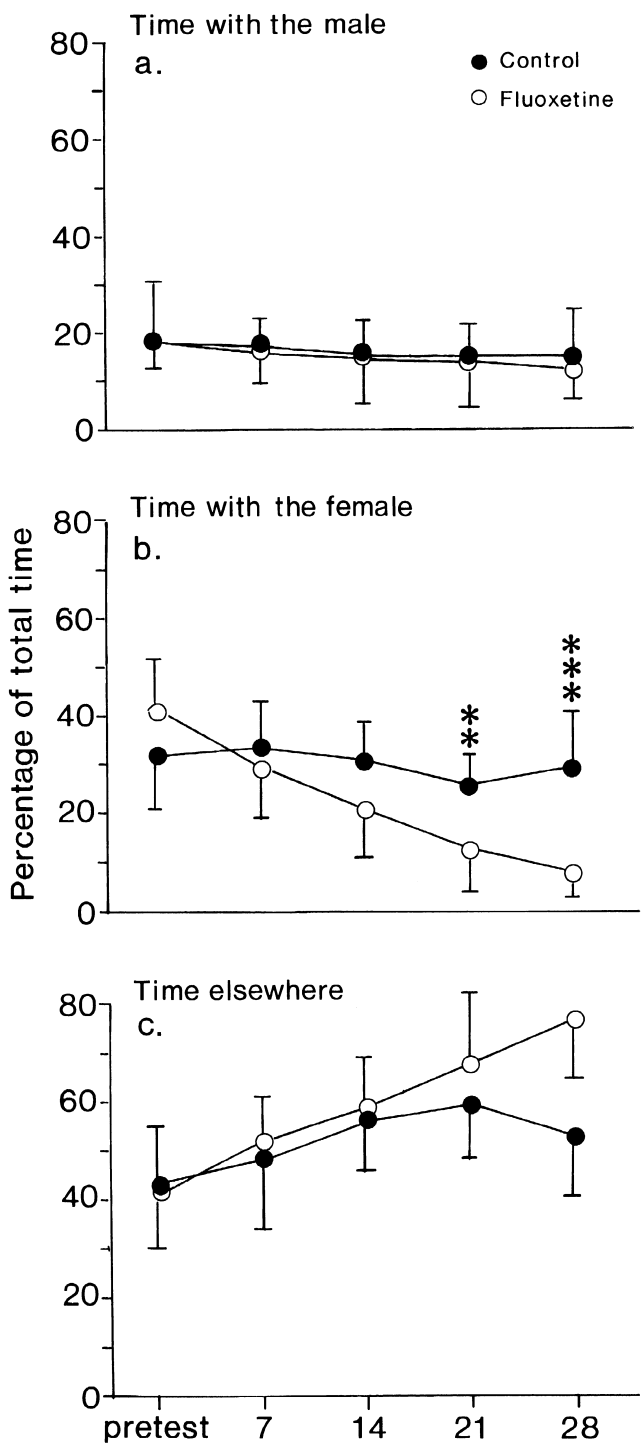

FIG. 1. Percentage of total test time (medians ± interquartile range) spent by sexually experienced males (a) in the vicinity of a sexually active male, (b) in the vicinity of an estrous female, and (c) elsewhere. The rats had been treated daily with fluoxetine (10 mg/kg) (white dots) or saline (black dots) for 7, 14, 21, or 28 days. Stars indicate comparisons between groups; $^{**}p < 0.02$, $^{***}p < 0.01$.

tency), and time from ejaculation to the following intromission (postejaculatory interval). The observations were terminated when one of the following conditions was fulfilled: (a) when no intromission occurred within 15 min after the presentation of the female, (b) when the male did not ejaculate within 30 min from the first intromission, (c) after the first intromission following ejaculation, and (d) if no further intromission had taken place 15 min after the ejaculation.

Drug Treatment

Fluoxetine HCl (Eli Lilly Co., Indianapolis, IN) was dissolved in saline and administered subcutaneously at the same time every day (given volume: 2 ml/kg). Behavioral experiments always started 3 h after drug administration.

Statistics

Comparisons between groups were performed by the Mann–Whitney *U*-test (behavior) and *t*-test (body weight). Within-group comparisons (behavior) were performed by the Wilcoxon test. $p < 0.05$ was considered significant (two tailed).

Experimental Design

Experiment 1. In experiment 1, male rats were administered fluoxetine (10 mg/kg, SC) ($n = 23$) or saline ($n = 23$) for 28 days. The rats were tested for sexual motivation before drug treatment started and after 7, 14, 21, and 28 days of treatment. The drug was always given 3 h before the test was started.

Experiment 2. In experiment 2, male rats were administered fluoxetine (10 mg/kg, SC) ($n = 20$) or saline ($n = 20$) for 14 days. The copulatory behavior of the animals was studied before treatment and after 3, 6, 9, and 13 days of drug treatment. In addition, the sexual motivation was assessed before treatment and on day 14. The drug was always given 3 h before the test was started.

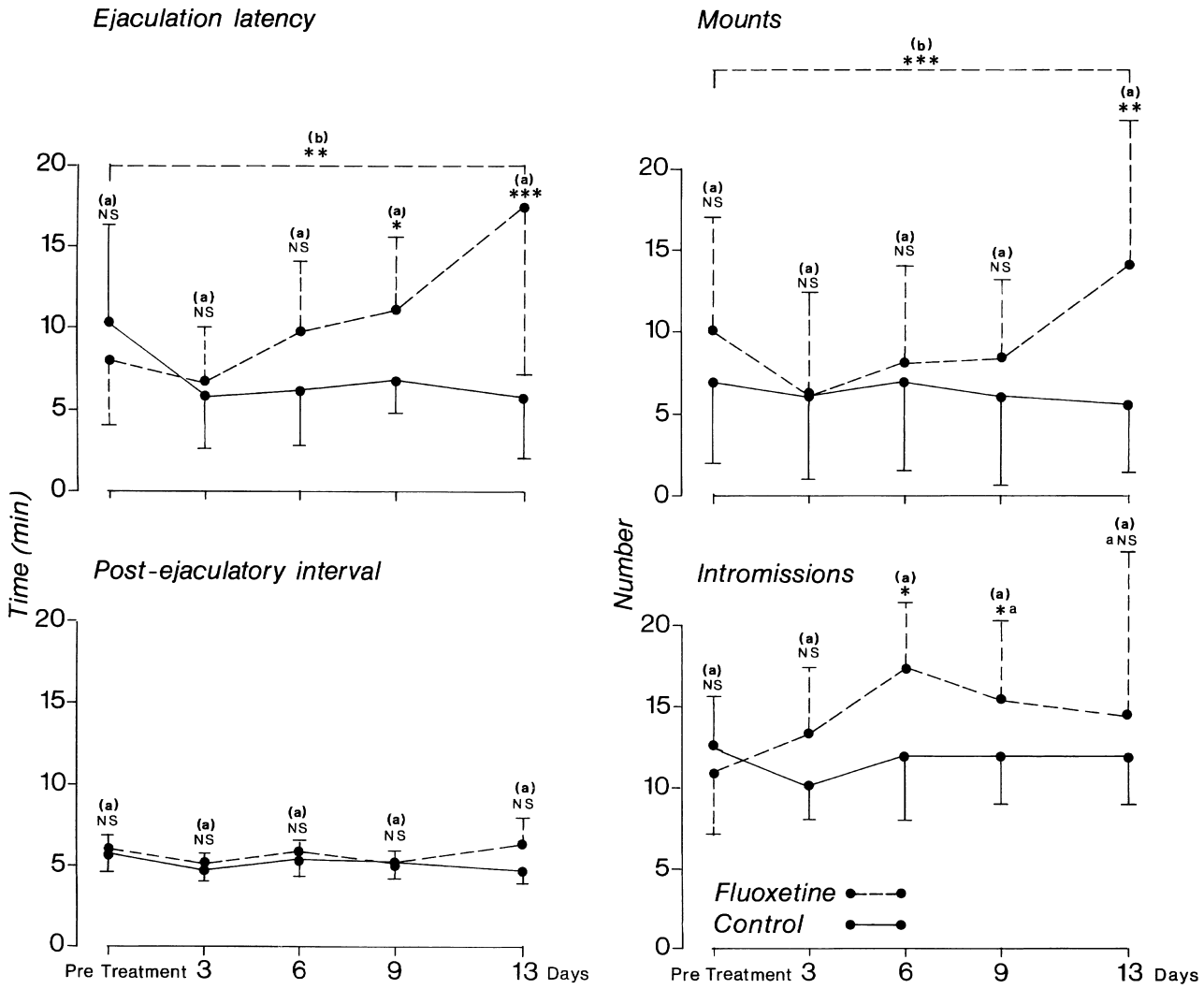

FIG. 2. Sexual behavior displayed by male rats after 3, 6, 9, and 13 days of treatment with fluoxetine (10 mg kg−1) (dotted) or saline ($n = 20$) or saline ($n = 19$) (medians ± interquartile range). Statistical analysis was performed by the Friedman two-way ANOVA followed by comparisons between groups (a) (Mann–Whitney *U*-test) and within group (b) (Wilcoxon signed rank test). $^{*}p < 0.05$, $^{**}p < 0.02$, $^{***}p < 0.01$.

RESULTS

Experiment 1

The effect of 28 days of treatment with fluoxetine on sexual motivation is shown in Fig. 1. Untreated male rats showed female-oriented preference; i.e., they spent significantly more time in the vicinity of the female rat than in the vicinity of the male rat or elsewhere. During treatment with fluoxetine, the time spent by the male rats in the vicinity of the female rat was progressively reduced; after 3 weeks of treatment, the rats showed no preference for the female.

Experiment 2

As shown in Fig. 2, subchronic administration of fluoxetine to male rats induced a progressive increase in ejaculatory latency; this effect reached statistical significance (vs. controls) at day 9. After 13 days of treatment, total number of mounts was also significantly increased in fluoxetine-treated rats.

Figure 3 shows the results of the tests for sexual motivation. Both groups of animals spent significantly more time near the female; before treatment, no differences were seen between the groups. After 14 days of treatment with fluoxetine, these animals still showed a clear preference for the female; however, when compared to saline-treated controls, they spent significantly less time near the female. The time the animals spent elsewhere did not differ between the groups.

Effect on Weight

Subchronic administration of fluoxetine to male rats reduced the normal increase in body weight (fluoxetine 22 days: 336 ± g, controls: 363 ± 4 g, $p < 0.01$) (mean ± SEM; Student's *t*-test).

DISCUSSION

In the present study, sexual motivation was measured as the level of interest for a stimulus in a two-choice situation involving a male and an estrous female. Several studies conducted in our laboratory have demonstrated that sexual motivation is required for this choice to be made. Thus, castrated male rats fail to respond to any of the sexual stimuli presented to them, and show a renewed interest for the female after treatment with testosteron (38). Furthermore, the interest for the estrous female is drastically increased in males made sexually aroused by repeated intromissions and, conversely, decreased in sexually exhausted males (37).

A large number of reports suggest that serotonin reuptake inhibitors may reduce libido in humans (for reference see the introductory paragraphs). The major purpose of this study was to investigate whether subchronic administration of an SSRI also influences sexual motivation in rats. The assumption that SSRIs do reduce sexual drive in male rats was supported by the finding that administration of fluoxetine (15) for 2–4 weeks markedly reduced the time spent by a sexually experienced male rat in the vicinity of an estrous female. The drug treatment did not increase the time spent with the male; thus, sexual orientation was not influenced by the treatment.

To our knowledge, this is the first study showing an effect of SSRIs on sexual motivation in rats. In a separate experiment, we have found that subchronic administration of another SSRI—citalopram—also reduces the time spent by a male rat in the vicinity of a female (data not shown). On the other hand, both these experiments contrast to a recent study

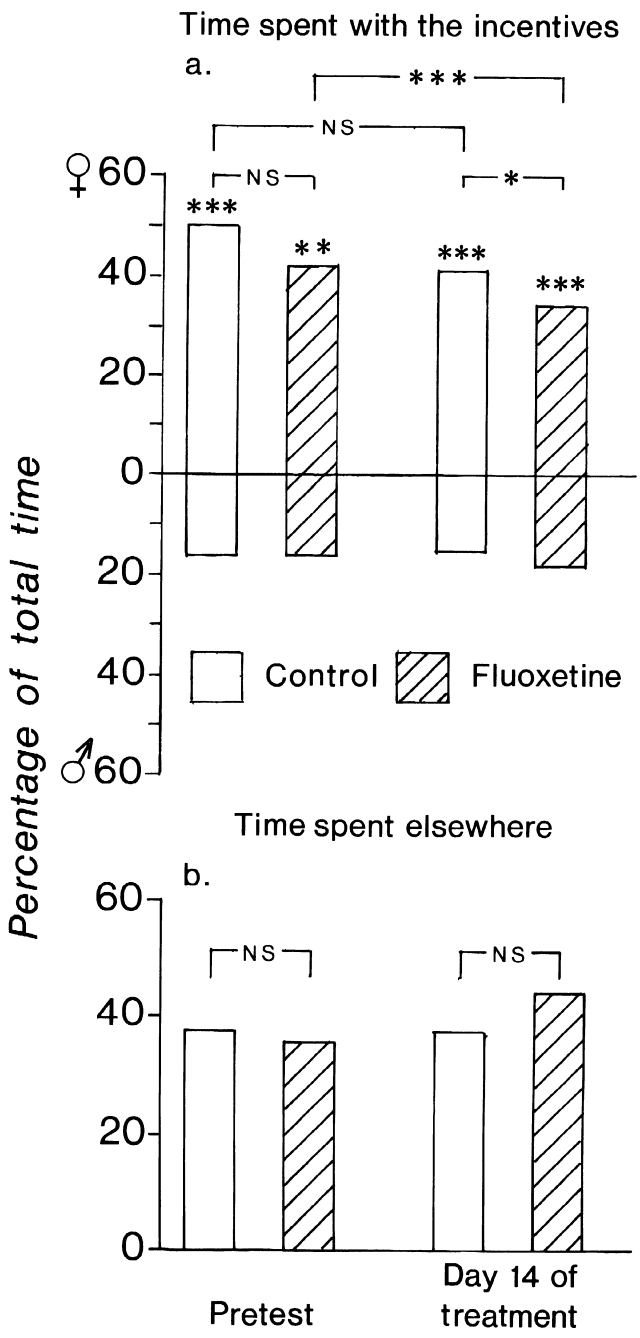

FIG. 3. Median percentage of total test time spent by sexually experienced males (a) in the vicinity of a sexually active male or an estrous female, and (b) elsewhere. The rats had been treated daily with fluoxetine (10 mg/kg) or saline for 14 days. Stars indicate comparisons within-group and (+) indicates between-group comparisons; $*p < 0.05$, $**p < 0.02$; $***p < 0.01$.

by Taylor and co-workers (35) showing no effect of fluoxetine on sexual motivation in male rats; however, in that study, the dose of fluoxetine was considerably lower (0.75 mg/kg) than in the present experiment.

The multiple effects and side effects of SSRIs in humans differ considerably with respect to onset of action. Thus, whereas SSRI-induced nausea and anxiety are immediate in

onset, and short to fade away, most therapeutic effects of the drugs have an onset of action of several weeks. The present data suggest that the effect of SSRIs on sexual motivation—in contrast to SSRI-induced nausea and anxiety—is characterized by a certain time lag and that it is not the subject of a short-term tolerance. The onset of action of SSRI-induced reduction in libido in humans has, to our knowledge, not been thoroughly studied.

Not only sexual motivation but also the copulatory behavior was influenced by fluoxetine administration; thus, a significant increase in ejaculatory latency was observed in rats administered fluoxetine for 9 or 13 days (but not in rats given fluoxetine for 3 days only). The progressive increase in number of mounts and in ejaculation latency accompanying the drug treatment may both be taken as evidence for a lowered sexual motivation (23,24). Indeed, both with respect to the consummatory and the motivational aspects of sexual behavior, the effects of subchronic administration of fluoxetine began to appear at approximately the same time.

An effect of serotonin reuptake inhibitors on ejaculatory latency in rats is in line with previous studies (2,35,39,40), and is also in consonance with clinical reports suggesting that SSRIs may cause prolonged ejaculation latency as a side effect, and may be of benefit for the treatment of ejaculatio præcox (for reference see the introductory paragraphs). The lack of effect of acute administration of fluoxetine on ejaculatory latency contrasts the study of Taylor and co-workers (35), in which one single dose of fluoxetine increased time to ejaculation in male rats. This difference in results may be due to differences in drug regimen—in the present study the drug was given 3 h before the behavioral experiments started—or by differences between the rats, for example, with respect to sexual experience. Most clinical studies suggest that subchronic administration of SSRIs (2–4 weeks) are needed to increase the ejaculation latency in patients with ejaculatio præcox (25,26); however, in one controlled trial, the strong (but nonselective) serotonin reuptake inhibitor clomipramine, taken as a single dose 1 h before coitus, was reported more effective than placebo (18).

Previous studies suggest that sexual behavior in male rats is inhibited by serotonin. Thus, whereas an increase in central serotonin activity, as obtained by the administration of the serotonin precursor 5-hydroxytryptamine (2) or of a monoamine oxidase inhibitor (1,33) is accompanied by a depression of male rat sexual behavior, a reduction in brain serotonergic neurotransmission, as obtained by the inhibition of tryptophan hydroxylase (1,33,34), or by chemical or mechanical lesions of serotonin neurons (4,11), facilitates male rat sexual behavior. Thus, the present observation, in conjunction with those by Ahlenius and co-workers (2), Yells and co-workers (39), and Taylor and co-workers (35), lends indirect support for the notion that subchronic administration of SSRIs does result in an increased output from serotonin synapses in the brain [see (12,14)].

Case reports and small open trials have suggested that the sexual side effects of SSRIs may be antagonized by coadministration of a 5 HT_2 receptor antagonist (3,6,30), an alpha-2 adrenoceptor antagonist (9,21), or by a dopaminomimetic (7,10,17). The similarity between rats and humans with respect to how sexual behavior is influenced by SSRIs should enable a more systematic evaluation of how these common and bothersome side-effects can be effectively counteracted.

ACKNOWLEDGEMENTS

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