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REVIEW

The Influence of Fluoxetine on Aggressive Behavior

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A large body of evidence from studies in humans, in nonhuman primates, and in smaller laboratory animals has supported a role for serotonin in the modulation of aggressive behavior. The evidence shows that diminished serotonergic function can be linked to aggressive behavior and that treatments that increase serotonergic function reduce aggression. Embedded in this large body of data are studies done specifically with fluoxetine, a serotonin uptake-inhibiting antidepressant drug suggested by some individuals charged with criminal aggression and by their attorneys to cause aggressive violence. Contrary to those charges, extensive studies of fluoxetine in animals have shown that fluoxetine decreases aggressive behavior in various species and models of aggression. Clinical studies of fluoxetine in aggressive behavior have been more limited, but findings in those studies seem consistent with the anti-aggressive effects of fluoxetine found in animal studies. ***[Neuropsychopharmacology 14:77–81, 1996]***

KEY WORDS: *Fluoxetine; Serotonin; Aggression; Muricidal behavior; p-Chlorophenylalanine*

One brain neurotransmitter that seems to influence aggressive behavior is serotonin. Reduced serotonin function has been associated with increased aggression in laboratory animals, and drug treatments to increase serotonin function have reduced aggressive behavior in animals, as reviewed in previous publications such as Valzelli (1982), Pucilowski and Kostowski (1983), Olivier et al. (1987), and Miczek and Donat (1989). Eichelman (1990) has emphasized the congruence of findings in humans and in laboratory animals in regard to the role of serotonin in aggression. Information continues to accumulate supporting a role of serotonin in modulating aggression, as exemplified by some of the studies to be cited and by a recent paper reporting a genetically engineered strain of mouse lacking a specific serotonin receptor (the $5HT_{1B}$ receptor), the prominent behavioral abnormality being increased aggression (Saudou et al. 1994).

This review focuses on one particular drug that increases serotonin function, fluoxetine, a serotonin uptake inhibitor. Fluoxetine (Prozac) has become the most widely used antidepressant drug in the world. Because many patients receive fluoxetine, it is inevitable that some criminal acts involving violent aggression have been committed by individuals while they are taking fluoxetine. In some such cases the claim has been made that Prozac caused the violent aggression. Such claims seem to have come in all cases from offenders or their attorneys, not from medical practitioners, and are contrary to the large body of evidence showing that fluoxetine decreases aggressive behavior in animals and possibly in humans.

SEROTONIN AND AGGRESSIVE BEHAVIOR

In humans and in nonhuman primates decreased serotonergic function inferred from low cerebrospinal fluid levels of the serotonin metabolite 5HIAA (5-hydroxyindoleacetic acid) or from pharmacological probes is reported to be associated with violent or aggressive be-

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havior (Brown and Linnoila 1990; Coccaro et al. 1989; Coccaro 1992; Mehlman et al. 1994; Siever and Trestman 1993). In smaller animals brain concentrations of serotonin, rather than cerebrospinal fluid concentrations of its metabolite, have been measured. In wild Norway rats (Popova et al. 1991b) and in silver foxes (Popova et al. 1991a) serotonin concentrations in several brain regions were found to be higher in nonaggressive animals than in aggressive animals. In other laboratory animals treatments that decrease serotonergic function increase aggressive behavior, whereas treatments that increase serotonergic function decrease aggressive behavior. Some examples of drugs that increase serotonin function and have been reported to decrease aggressive behavior include serotonin uptake inhibitors—indalpine (Molina et al. 1986) and citalopram (Molina et al. 1987); direct-acting serotonin agonists, eltoprazine (Olivier et al. 1987), quipazine (Gibbons et al. 1978b; Datla et al. 1991), and 5-methoxy-N, N-dimethyltryptamine (Molina et al. 1986; and 8-hydroxy-2-(di-n-propylamino)tetralin (Molina et al. 1986, 1987); and serotonin precursors—tryptophan (Gibbons et al. 1978b; Raleigh et al. 1991; Wagner et al. 1993) and 5-hydroxytryptophan (Datla et al. 1991; Gibbons et al. 1978a). Some examples of treatments that decrease serotonin function and have been reported to increase aggressive behavior include serotonin receptor antagonists—cyproheptadine (Raleigh et al. 1991) and ketanserin (Datla et al. 1991); the inhibitor of serotonin synthesis, p-chlorophenylalanine (Gibbons et al. 1978a; Berzsenyi et al. 1983; Molina et al. 1987; Datla et al. 1991), the serotonin-depleting drug fenfluramine (Gibbons et al. 1978b; Raleigh et al. 1991); and lesions of raphe nuclei (Molina et al. 1987). Many of the studies were done in muricidal rats, but some have been done in other models and other species (see also reviews cited).

FLUOXETINE EFFECTS ON AGGRESSIVE BEHAVIOR IN ANIMALS

Drug effects on many types of aggressive behavior measured in various laboratory animal species have shown that drugs that increase serotonin function directly by activating serotonin receptors or indirectly by increasing serotonin availability, reduce aggressive behavior (e.g., Olivier et al. 1987). Among the drugs studied have been selective inhibitors of serotonin uptake, including fluoxetine.

Muricidal Behavior in Rats

One of the most common types of aggressive behavior studies in laboratory animals is muricidal (mouse-killing) aggression in rats. Muricidal behavior occurs spontaneously in some strains of rats and can be induced with certain drugs. Many types of drugs that increase brain serotonin function have been shown to reduce muricidal aggression in rats. The first report that fluoxetine inhibited muricidal aggression was by Gibbons et al. (1978b). Those investigators found that fluoxetine inhibited mouse-killing aggression in muricidal rats and that the same effect was produced by quipazine, a direct-acting serotonin receptor agonist, and by L-tryptophan, the amino acid precursor to serotonin.

Berzsenyi et al. (1983) reported that fluoxetine reduced mouse-killing aggression in rats made muricidal by treatment with p-chlorophenylalanine to inhibit serotonin synthesis. At the same dose (10 mg/kg IP), fluoxetine decreased 5HIAA concentration in eight brain regions studied. The decrease in 5HIAA concentration is one neurochemical marker for uptake inhibition, the decrease resulting from a compensatory reduction in serotonin turnover in response to increased extracellular concentrations of serotonin (Fuller 1994; Fuller and Wong 1977).

Kostowski et al. (1984) reported that fluoxetine inhibited spontaneous and p-chlorophenylalanine-induced muricidal aggression in rats. Unlike two other antidepressant drugs, nomifensin and desipramine, which caused visible behavioral and autonomic alterations at doses that suppressed muricide, the gross behavior of rats treated with fluoxetine was not altered except for the reduction in muricidal aggression. The fluoxetine-treated rats were described as "calm with no signs of overt sedation or drowsiness, responding normally to the usual stimuli."

Stark et al. (1985) found that fluoxetine dose-dependently decreased mouse-killing aggression in spontaneously muricidal rats at doses that blocked serotonin uptake in rat brain and produced other functional effects indicative of increased serotonergic neurotransmission.

Molina et al. (1986) reported that fluoxetine reduced muricidal aggression induced in rats by social isolation or by olfactory bulb ablation. The effect of fluoxetine was mimicked by indalpine, another serotonin uptake inhibitor, and by two direct-acting serotonin receptor agonists, 5-methoxy-N,N-dimethyltryptamine and 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT).

Molina et al. (1987) later studied rats that had been made muricidal either by treatment with p-chlorophenylalanine to inhibit serotonin synthesis or by electrolytic lesions of the dorsal and median raphe nuclei (rich in serotonin-containing neurons). Fluoxetine inhibited muricidal aggression in both groups of rats, as did another serotonin uptake inhibitor, citalopram and the direct-acting serotonin agonists 5-methoxy-N,N-dimethyltryptamine and 8-OH-DPAT.

Other Aggressive Behavior in Rats

In addition to muricidal aggression in rats, footshock-induced aggression in paired rats has also been reported to be decreased by fluoxetine. Datla et al. (1991) studied latency to fight, total period of physical contact, and cumulative aggression scores in these rats. Fluoxetine attenuated footshock-induced aggression by all three measures, as did quipazine, a direct-acting serotonin receptor agonist. The inhibitor of serotonin synthesis, p-chlorophenylalanine, increased all measures of footshock-induced aggression, as did ketanserin, a serotonin receptor antagonist.

Aggressive Behavior in Mice

Richard J. Katz at the University of Michigan (personal communication 1977; cited by permission) first observed that fluoxetine decreased intraspecies aggression in male mice that had become aggressive because of social isolation for ten days. Wagner et al. (1993) studied alcohol-induced aggression in mice fed a standard diet or a diet supplemented with tryptophan. Fluoxetine reduced resident-intruder aggression in these mice, and the tryptophan-rich diet potentiated the effect of fluoxetine, supporting the interpretation that increased serotonergic function was the mechanism of its action.

Aggressive Behavior in Hamsters

Ferris and Delville (1994) found that a microinjection of arginine vasopressin into the ventrolateral hypothalamus in male golden hamsters facilitated offensive aggression in a resident-intruder model and that fluoxetine inhibited that aggression. In yet-unpublished studies Ferris and colleagues (personal communication 1994; cited by permission) have found that fluoxetine inhibits spontaneously occurring offensive aggression in these hamsters (not treated with arginine vasopressin) at doses that inhibit serotonin uptake and increases extracellular serotonin concentration measured by microdialysis of the hypothalamus in these hamsters.

Aggressive Behavior in Monkeys

One of the most interesting descriptions of fluoxetine effects on aggressive behavior in animals was published by Raleigh and coworkers at UCLA (1991), who studied the social behavior of monkeys living in troops in a natural habitat. Each troop consisted of three adult male monkeys, three or more adult female monkeys, and the offspring, which varied in number. In each troop, one male monkey is always the dominant member of the troop. The experiment these investigators did was to remove the dominant male monkey and observe which of the two remaining male monkeys became dominant during the ensuing weeks. At the time of removal of the previously dominant male, drug treatment of the two remaining males began. One male was treated with a drug to affect serotonin function, and the other male was treated with placebo. Two drugs were used to increase serotonin function, fluoxetine, a serotonin uptake inhibitor, or tryptophan, a serotonin precursor. Two drugs were used to decrease serotonin function, fenfluramine, a serotonin depletor, or cyproheptadine, a serotonin receptor antagonist. Twelve experiments were done. In all cases the monkey treated with a drug that increased serotonin function became dominant over the placebo-treated monkey. And in all cases the monkey treated with placebo became dominant over the monkey treated with a drug that decreased serotonin function. In other words, greater serotonin function led to dominance in the male. The investigators discussed in depth the distinction between dominance and aggression. They measured various specific behaviors in these monkeys, using a previously established rating scale. The findings showed that fluoxetine treatment of male monkeys increased positive social interactions and decreased aggressive behavior in those monkeys. The monkeys became dominant, not by being aggressive, but by enhanced social interactions with the other monkeys. Exactly the same thing happened with tryptophan. In direct contrast, monkeys treated with cyproheptadine or fenfluramine became more aggressive, showed fewer positive social interactions, and became subordinate to the placebo-treated male monkeys.

FLUOXETINE EFFECTS ON AGGRESSIVE BEHAVIOR IN HUMANS

Based on the accumulated evidence that serotonin is an important neurotransmitter in aggression and that drugs that increase serotonin function decrease aggressive behavior in many animal models, Charney et al. (1990) suggested that serotonin uptake inhibitors may be particularly efficacious for depressed patients at risk of violent suicide because of the evidence that such patients may have diminished serotonin function. Charney et al. (1990) also suggested that patients with impulse and aggressive personality disorders may have a similar dysfunction and hence may also respond to serotonin uptake inhibitors. Only a few small studies of fluoxetine effects on aggressive behavior have been done in humans, but some investigators have reported that fluoxetine does seem to decrease various kinds of aggressive behavior in humans.

Coccaro et al. (1990) studied three personality disorder patients. Fluoxetine treatment was associated

with a diminution in various clinician-rated and self-rated impulsive aggressive behaviors in these patients. The findings are consistent with similar beneficial effects reported by the same research group with another selective inhibitor of serotonin uptake, sertraline (Kavoussi et al. 1994).

Cornelius et al. (1991) studied five borderline personality disorder patients with severe symptoms who were previously resistant to drug treatment. Open treatment with fluoxetine for 8 weeks resulted in decreased depression, suicidality, and impulsivity scores, but hostility and psychotic symptoms did not change significantly.

Markowitz (1992) gave fluoxetine to 21 profoundly mentally retarded persons exhibiting aggression and self-injurious behavior. Marked improvement occurred in 13 patients, some improvement in 6 others, and only 2 patients showed no improvement. Positive changes occurred in the areas of self-injury, agitation, emotional lability, and aggression.

In addition to these prospective but relatively small studies, Heiligenstein et al. (1993) have done a comprehensive metaanalysis to investigate a possible association of fluoxetine with violence or aggression by examining clinical trial data collected in the United States during the initial therapeutic trials with fluoxetine. A total of 3,992 patients were included in studies of possible efficacy in depression, obesity, bulimia nervosa, obsessive-compulsive disorder, smoking cessation, and alcoholism. Heiligenstein et al. (1993) found that events suggestive of aggression (hostility, personality disorder, antisocial reaction) were four times more likely to occur in placebo-treated patients than in fluoxetine-treated patients.

Although large, prospective, double-blind controlled clinical trials of fluoxetine to determine its possible usefulness in treating aggressive behavior have not been conducted, the available data from human studies seem compatible with the extensive animal studies in which fluoxetine was shown to reduce several types of aggressive behavior in various species.

FLUOXETINE EFFECTS ON ANGER IN HUMANS

Unlike laboratory animals in which only aggressive behavior can be studied, feelings as well as aggressive behavior can be studied in humans. There are now a few reports that fluoxetine reduces feelings of anger in humans.

Fava et al. (1993) studied 85 outpatients suffering from major depression. Initially, 44% of these patients exhibited anger attacks, defined as sudden, intense spells of anger associated with a surge of autonomic arousal including such symptoms as tachycardia, sweating, flushing, and a feeling of being out of control. After 8 weeks of open treatment with fluoxetine, the anger attacks disappeared in the majority (71%) of patients who had previously reported them. The investigators concluded that fluoxetine treatment appears to be beneficial in reducing anger and hostility in this subgroup of depressed patients, confirming an earlier report by the same investigators (Fava et al. 1991).

Weinman and Ruskin (1994) described a case report of a male patient suffering poststroke depression in whom uncontrollable anger attacks was a common and major symptom. After fluoxetine treatment, the intensity and frequency of his anger attacks were reduced along with episodes of aggressive behavior.

Salzman et al. (1995) have recently described a 13-week double-blind study in volunteer subjects with mild to moderately severe borderline personality disorder. The most striking finding from the study was a decrease in anger among 13 fluoxetine recipients compared to 9 placebo recipients. The decrease was described as clinically and statistically significant.

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