Pharmacology Biochemistry and Behavior, Vol. 63, No. 3, pp. 435–440, 1999

0091-3057/99/$–see front matter

PII S0091-3057(99)00044-1

Feeding and Reward Interactions From Chronic Paroxetine Treatment

ANNE T. M. KONKLE AND CATHERINE BIELAJEW

School of Psychology, University of Ottawa, Ottawa, Ontario, K1N 6N5, Canada

Received 28 August 1998; Revised 11 December 1998; Accepted 22 December 1998

KONKLE, A. T. M. AND C. BIELAJEW. *Feeding and reward interactions from chronic paroxetine treatment.* PHARMACOL BIOCHEM BEHAV **63**(3) 435–440, 1999.—The self-stimulation paradigm was used to evaluate threshold changes following acute and chronic administration of the selective serotonergic reuptake inhibitor paroxetine; stimulation sites were located in medial forebrain bundle structures. Rats received daily systemic injections of one of three doses of paroxetine (2.5, 5, or 7.5 mg/kg), either with or without stimulation, while the last group received the same number of vehicle injections with stimulation. Frequency thresholds were collected over a period of 6 h on day 1 (acute phase); no marked difference in the values were observed over this time span. Thereafter, the animals were tested every third day (chronic phase), for a total of 11 sessions or roughly 31 days. Commencing around day 10 of the drug treatment, the higher dose of paroxetine produced a significant and persistent facilitation in self-stimulation thresholds, mimicking the delay in clinical response in humans that is well documented. We also monitored on a daily basis the animals' weights and food intake. A large difference in the percent efficiency of food utilization, measured by calculating the ratio of weight change to food intake, was observed between the animals receiving stimulation and those that were not, exclusive to the higher dose of paroxetine. The percent efficiency of food utilization remained low in the animals only receiving the drug treatment, whereas they returned to baseline levels and above in subjects receiving both paroxetine and stimulation. Two findings emerge from these data: 1) the paradigm appears to model the human response to this class of antidepressants, and 2) rewarding stimulation seems to counteract the drug-induced weight loss. © 1999 Elsevier Science Inc.

Paroxetine Antidepressants SSRI Weight Brain stimulation reward Feeding Medial forebrain bundle

THE monoamine hypothesis of depression states that this condition is caused by a functional deficit of monoaminergic neurotransmitters at certain sites in the brain (10,37). Support for this idea first came from the observation that monoamine antagonists could induce a depressive state (17,36), and was further strengthened by pharmacological evidence that effective antidepressants facilitate norepinephrine and serotonin neurotransmission (10,37). While earlier studies concentrated mostly on abnormalities of these neurotransmitter systems, recent work suggests that dopamine may play a role in the delay of onset of the therapeutic action of antidepressants, by way of recently characterized subtypes of dopamine receptors (9).

The treatment of depression has changed over the years as awareness of the etiological basis of the disease has grown. The monoamine oxidase inhibitors were thought to be the most suitable treatment for depression when the more general monoamine hypothesis involving serotonin, norepinephrine, and dopamine prevailed. The hypothesis progressed to exclude dopamine, where the tricyclic antidepressants predominated, and finally to the exclusivity of serotonin, where the selective serotonin reuptake inhibitors (SSRI) were introduced as the choice pharmacological treatment for depression (25). The SSRIs increase the synaptic concentration of serotonin by desensitizing presynaptic serotonin autoreceptors on serotonin nerve terminals (3,6,14,18,23). Among this class of drugs, we find paroxetine (Paxil®), sertraline (Zoloft®), fluoxetine (Prozac®), and venlafaxine (Effexor®), presented in decreasing order of selectivity for serotonin (31). The drug's overall selectivity is also influenced by the action of its metabolites with the serotonin receptors. The central and autonomic side effects associated with tricyclic antidepressants are not observed with the selective serotonin reuptake inhibitors, due to their reduced interaction with muscarinic cholinergic and histaminergic receptors (12).

There are several animal models that aim to simulate a depressed state within which to investigate aspects of depression, including among them the intracranial self-stimulation paradigm (5). This model of depression is based on the obser-

Requests for reprints should be addressed to Catherine Bielajew, School of Psychology, University of Ottawa, 11 Marie Curie, Ottawa, Ontario, K1N 6N5, Canada.

vation that a central symptom of depression is a decreased capacity to experience pleasure, and the assumption is that interventions that relieve symptoms of depression in humans, such as antidepressant drugs, will boost reward transmission, translating into a reduction in the threshold required to maintain self-stimulation responding in rats.

Overall, the tricyclic antidepressants when administered chronically tend to produce small or unremarkable decreases in reward threshold, as assessed using either the curve shift paradigm or other methods that do not rely on a simple rate-of-response to scale the effect (11,15,26,27,43). However, there appears to be very little literature that deals specifically with the effects of a chronic challenge of agents with SSRI properties on thresholds for brain stimulation reward (24). Thus, the aim of this study was to assess the threshold consequences of acute and chronic administration of the compound, paroxetine, an SSRI of importance in the clinical management of depression.

Paroxetine is primarily metabolized in the liver, and none of its metabolites appear to be active (23). The most common side effects associated with paroxetine intake are somnolence and gastrointestinal dysfunctions such as nausea and a reduced appetite (7,23). A few cases of akathisia and bleeding, which are attributed to the intake of paroxetine, have been reported (1,32), although these effects are not apparent in all individuals treated with paroxetine. For these reasons, we included a group of animals that received paroxetine alone and no stimulation in order to distinguish the drug's influence on weight change from potential weight changes due to an increased activity level.

METHOD

Subjects and Surgical Procedure

Three male Long–Evans and 32 male Sprague–Dawley rats (Charles River Laboratories) weighing between 355–420 g at the time of surgery were individually housed in plastic cages and were allowed free access to tap water and Purina rat chow. The animals were maintained on a 12-h light–dark cycle with light onset at 0700 h.

Stereotaxic surgery was conducted as follows: each rat was anesthetized with 65 mg/kg intraperitoneally of sodium pentobarbital (Somnotol®) and when judged necessary, the animal was administered a 0.05 ml intramuscular injection of xylazine (Rompun®). To avoid discomfort due to pressure from the ear and incisor bars, a local anesthetic, lidocaine hydrochloride (Xylocaine® 2%), was topically applied inside the rats' ears and just behind the upper incisors. Their eyes were covered with ophthalmic ointment (BNP)to prevent dryness. To avoid mucus buildup in the lungs, a subcutaneous injection was given either of 0.4 ml of glycopyrrolate (Robinul®) or 0.05 ml of atropine.

Monopolar stainless steel fixed electrodes, insulated with Epoxylite, except at the tips, were implanted in the medial forebrain bundle bilaterally at the level of the lateral hypothalamus (LH) or unilaterally at the level of the ventral tegmental area (VTA). The flat skull coordinates, based on the rat brain atlas (34), were 2.6–3.0 mm posterior to bregma, 1.6–1.7 mm lateral to the midsaggital suture, and 8.2–8.4 mm below dura for the lateral hypothalamus, and 4.8 mm posterior to bregma, 1.0 mm lateral to the midsaggital suture, and 8.2–8.3 mm below dura for the ventral tegmental area. A gold amphenol pin soldered to a fine stainless steel wire that was wrapped around four jewellers' screws anchored in the skull, served as the current return. Dental acrylic was used to firmly secure the entire assembly to the skull.

Behavioral Testing

All behavioral tests were conducted in a wood and Plexiglas chamber with dimensions of 27 × 37 × 51 cm. A rodent lever was fixed 3.5 cm above the floor on the lower right wall of the chamber. Stimulation was supplied by a constant-current amplifier (30) and an integrated circuit pulse generator; the current was monitored continuously on an oscilloscope. Each lever press resulted in a 0.5 s train of square wave monophasic cathodal pulses, 0.1 ms in duration. Once the current was selected, the stimulation parameters remained fixed except for the frequency, which was varied according to the protocol described below.

Following a recovery period of 7 days postsurgery, the rats were trained to lever press using conventional shaping techniques. Starting with the minimum stimulation parameter values found to support maximum rates of responding (e.g., a combination of 200 μA and 40 Hz), the current was held constant and the frequency decreased by 0.1 $\log_{10}$ units per trial until little or no responding was observed. A 30-s pause separated each 60-s trial. The beginning of each trial was signalled by five trains of priming stimulation (one train per second) at the same parameter values as the subsequent 60 s trial. The frequency threshold was calculated by interpolation of the rate-frequency function and corresponded to the frequency associated with one-half of the maximum rate. This entire procedure was repeated at a second current, set at a value 0.2 $\log_{10}$ units greater than the first (e.g., 200 and 320 μA). During each session, which lasted roughly 45 min, four frequency thresholds were determined per current; the first one was considered a warmup and was, therefore, discarded. The presentation of the two currents was alternated from session to session. Lever pressing was deemed stable for each rat when the frequency thresholds did not vary by more than 0.1 $\log_{10}$ units for each current for 3 consecutive days.

Once the animals were thus stabilized, they were then randomly assigned to one of seven groups. There were two conditions overall: 1) drug and stimulation, and 2) drug without stimulation. Hence, four of the groups received drug (either 0, 2.5, 5.0, or 7.5 mg/kg) and stimulation sessions, while the remaining three groups received a dose of either 2.5, 5.0, or 7.5 mg/kg but no stimulation. All animals were handled similarly, starting at their time of arrival except for the stimulation distinction. The activity of all animals was monitored before and after drug injections, which included daily chronicling of weight and food intake; these values were then converted to percent efficiency of food utilization by dividing the mean value of weight change (g) over 3 days by the mean value of food intake (g) over the same period.

Drug Treatment

Paroxetine was donated by SmithKline Beecham Pharmaceuticals (Oakville, Ontario, Canada). The powdered compound was dissolved in 21% dimethyl sulphoxide (DMSO). This concentration was needed to dissolve the highest dose of paroxetine; concentrations greater than this have been reported to be used without deleterious effects (28,44). The animals received daily IP injections of the filtered paroxetine solution at a dose of either 2.5, 5.0, or 7.5 mg/kg for a duration of 31 days. The control group (0 mg/kg) received daily IP injections of 1 ml/kg of filtered DMSO in water.

The day prior to commencing drug treatment a baseline frequency threshold value was obtained at both currents for each rat. On the first day of drug treatment (acute phase), immediately following injection, each animal was tested at both

currents (see earlier description) once an hour for a total of 6 consecutive hours. Thereafter, chronic tests were conducted once every third day, approximately 4–6 h postinjection, to avoid any stress-related effects of injection and because the thresholds determined in the acute phase were observed to be most stable at this period. In summary, animals received 31 consecutive days of drug injections, during which self-stimulation sessions were conducted a total of 10 times.

Histology

After testing was completed, the animals were given a lethal dose of sodium pentobarbital. A necropsy was performed to evaluate the condition of the internal organs, because paroxetine is metabolized in the liver. The rats were then perfused intracardially with saline followed by 10% formalin. The brains were removed and stored in 10% formalin for at least 48 h; they were then frozen at −20° and sectioned at a thickness of 40 μm and stained with thionin. The location of the electrode tips was determined by aid of an atlas (34).

Statistical Analysis

Mean frequency thresholds for baseline and drug data of the animals receiving stimulation were determined at both currents for each of the six testing sessions in the acute phase and for each of the additional 10 sessions in the chronic phase. Recall that in the acute phase, sessions were conducted once every hour on the first day of drug treatment, whereas in the chronic phase, sessions were once a day, every third day of drug treatment. The $\log_{10}$ change in frequency threshold was then tabulated for each group. The mean threshold values were analyzed using a mixed ANOVA design with three factors—one independent (dose), and two repeated (current and session)—the latter with Huynh-Feldt corrections. To compare the total amount of stimulation across animals, a mean charge value was calculated from the frequency thresholds for each animal in the chronic phase of the experiment, using the equation where Q is the charge in μC (microcoulombs), I is the current in μA, N is the number of pulses in the stimulation train, and d is the pulse duration in seconds (13).

$$Q = IN\,d$$

To ascertain any performance effects induced by paroxetine, the maximal response rates recorded during the chronic phase of the experiment were analyzed using the same ANOVA design as above.

A similar analysis was carried out on the data pertaining to the efficiency of food utilization; in this case, the two factors were the groups (dose ± stimulation) and treatment sessions.

RESULTS

Figure 1 shows the tracings of the atlas plate (34) that best correspond to the sections containing the electrode tips, all of which were located within the limits of the medial forebrain bundle.

Histological results are not available for rats # 990 and 1184.

The analysis on the rate data yielded no significant difference between any of the groups or sessions.

The currents that were used to test the animals ranged from 200 to 500 μA, giving rise to overall charge values of 0.85 ± 0.41 for the low currents and 0.91 ± 0.40 for the high ones. Note that the variability does not reflect unstable thresholds, but rather changes in their values that accompanied the chronic drug regime. More importantly, the similarity in the charge values associated with low and high currents suggests good reciprocity between current and frequency. Finally, these values are consistent with what is usually observed with stimulation at these sites (13).

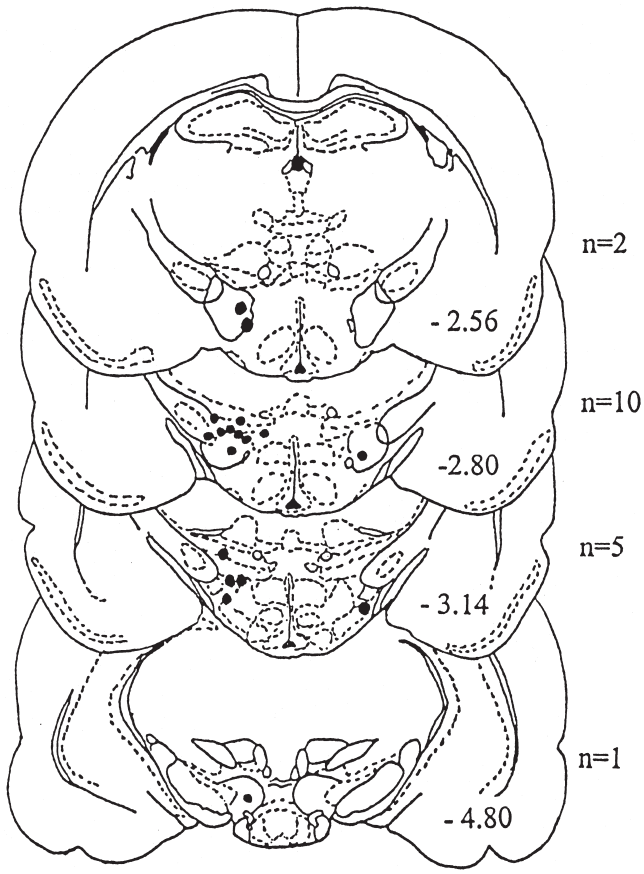

FIG. 1. Tracings from the atlas plates (34) that best correspond to the location of the electrode tips, shown by filled circles. The anteroposterior distance behind bregma and the number of subjects with tips found at that level are indicated on the right side of the figure.

Figure 2 shows the $\log_{10}$ change in frequency threshold on the first day (or acute phase) of drug administration. Each point and associated standard error represent the mean $\log_{10}$ change from baseline across five subjects, at 1-h intervals following an initial injection of paroxetine or vehicle (DMSO). The difference in $\log_{10}$ change in threshold from baseline and between the four groups are small, all less than 0.1 $\log_{10}$ units, suggesting no acute effect of paroxetine administration. Note, however, that of the 20 animals, approximately 20% of them, scattered throughout the four groups, did not readily self-administer stimulation during the first testing hour. The analysis of variance results indicate no main effect of either treatment or time, and no interaction of these two factors.

The $\log_{10}$ changes in thresholds for the chronic phase of the experiment are shown in Figure 3. Because neither the three-way interaction nor the main effect of current were significant, we chose to graphically represent the interaction between treatment and session that was significant, $F(28, 84) = 1.93$, $\alpha = 0.025$; the degrees of freedom were corrected for violations of the compound symmetry assumption using the Huynh-Feldt correction (19). Each point and associated standard error rep-

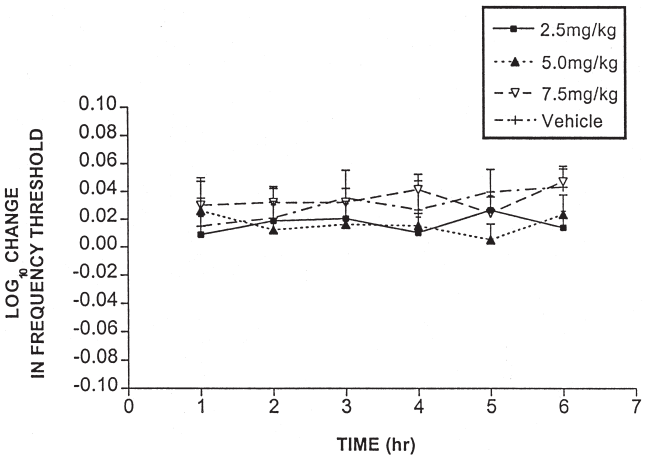

FIG. 2. The acute effects of systemic administration of different doses of paroxetine or vehicle on the $\log_{10}$ changes in frequency threshold. Each point represents the mean ± SEM of the thresholds collected for the five animals in each group. Negative values indicate a decrease in frequency threshold, interpreted as a facilitation in the rewarding value of the stimulation.

resent the mean $\log_{10}$ change from baseline for five subjects collapsed across both currents. Note that of these 20 subjects, five of them, from three of the four groups (vehicle, 5.0 and 7.5 mg/kg), were removed from the study at different times, beginning at session 5 (or the 13th day of the study), mostly due to implant loss; one animal was withdrawn when its weight loss reached 10% of its initial body weight. An effect of the higher dose (7.5 mg/kg) of paroxetine administration is apparent from this figure, as the difference in the $\log_{10}$ changes in threshold from baseline and between the paroxetine and vehicle groups continuously increases. The results of two linear contrasts revealed the 7.5-mg/kg group to be different from the other three groups at session 4, $F(1, 9) = 7.48$, $p < 0.025$, which is the last one to contain all five subjects in each group, and the final session (# 11) in which only three subjects remained in the 7.5-mg/kg group, $F(1, 9) = 8.58$, $p < 0.025$.

Figure 4 shows the percent efficiency of food utilization for groups receiving paroxetine, one dose with and the same dose without stimulation, as well as the group receiving the vehicle (DMSO) and stimulation. Most animals appeared healthy throughout drug treatment with respect to weight and food intake, whether or not they received stimulation. However, some of the animals receiving the highest dose of paroxetine without stimulation were removed from the study near its completion due to a weight loss greater than 10%.

The percent efficiency of food utilization is initially poor in all groups treated with paroxetine, reflecting weight loss and a decrease in food intake; however, it appears to return to normal by the third treatment session in all animals that were part of the lower dose conditions. Following the 31 days of drug treatment, all animals that remained in the study returned to near control values of percent efficiency of food utilization. The analysis revealed significant main effects of group, $F(6, 24) = 5.58$, $p < 0.001$, and session, $F(6, 133) = 11.03$, $p < 0.001$, with a Huynh-Feldt correction; we performed the analysis on 8 of the 10 sessions to include as much data as possible. A Dunnett's post hoc analysis was performed to evaluate the different patterns of efficiency between the stimulated and unstimulated animals receiving the highest dose of paroxetine. As is apparent from Fig. 4, the stimulated animals begin showing a significant improvement over their initially poor efficiency values around the third session, and this is maintained for the remainder of the study. The unstimulated animals show a small improvement in efficiency between sessions 3 and 6, after which it progressively deteriorates until the last session.

The necropsy report shows an increased occurrence in discoloration of the liver and kidneys as well as diffuse contouring of the liver lobes in most of the animals treated with paroxetine at a dose of 7.5 mg/kg (with and without stimulation) compared to the animals in all other groups.

Behavioral observations were noted each day during drug treatment. Before injection, the animals receiving the vehicle and the lower dose of paroxetine were very active, primarily

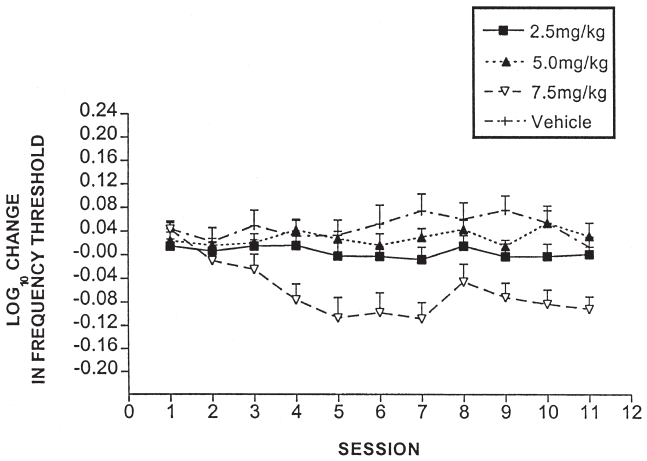

FIG. 3. The chronic effects of administration of paroxetine or vehicle on the $\log_{10}$ changes in frequency thresholds. Each point represents the mean ± SEM of the thresholds obtained for each group of five animals over two currents. A session was conducted every third day of drug treatment. Negative values indicate a decrease in the frequency threshold, interpreted as a facilitation in the rewarding value of the stimulation while positive values mean the reverse.

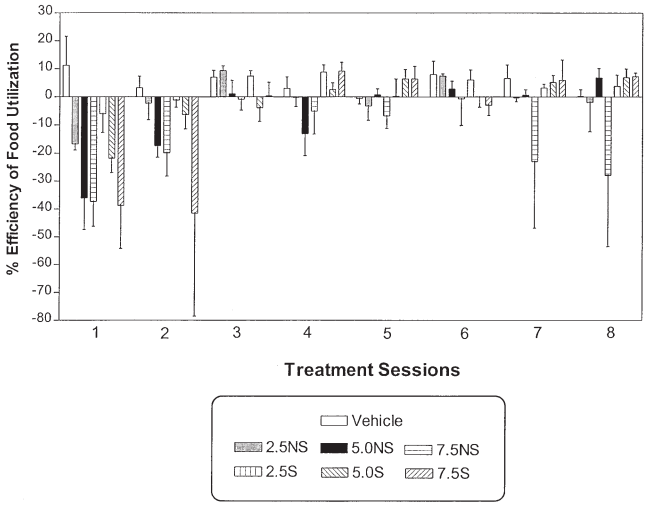

FIG. 4. The graph shows each group's % efficiency of food utilization (g wt change/g food intake). The results are expressed as cumulative group means ± SEM over each 3-day drug treatment session. The legend indicates the dose of paroxetine received with stimulation (S) or without stimulation (NS).

sniffing and rearing. They remained likewise after the injection, generally eating, drinking, grooming, or exploring their cages. Just before injection, the animals receiving the higher doses of paroxetine were very quiet, typically huddled in the back of their cages. Post injection, these animals would remain quiet, retreat to the back of their cages, and often lie down on their sides. Rarely would they exhibit any eating or drinking behavior immediately following the injection. Furthermore, some of the animals administered the higher dose of paroxetine developed hematomas in the lower abdominal cavity.

DISCUSSION

An important finding of this study is that chronic administration of paroxetine decreases frequency thresholds for self stimulation, which is interpreted as a facilitation in the rewarding value of the stimulation. Although some animals appeared sickly in their home cages where they were injected with paroxetine, the analysis of the rate data indicates that their self-stimulation performance was not compromised. The data show that the facilitation in thresholds begins at about the 10th day of drug treatment, similar to the well-documented delay in antidepressive effect reported in humans (8,20). In some animal studies, chronic desipramine administration has been shown to cause a gradual decrease in the required current necessary to support a fixed level of responding (11,27), although in one case this effect was only seen when an ascending, but not descending, current schedule was presented (11); when frequency rather than current was scaled in another report, no such effect was observed with the single dose tested (15). In a recent study (24), a chronic challenge of 5.0 mg/kg of fluoxetine (SSRI class of antidepressants) surprisingly gave rise to an increase in current threshold; it would be interesting to see if this finding persists with additional doses. The discrepancy in the results may also be due to differences in the behavioral techniques employed.

One possibility is that reward enhancement as measured by threshold will never be prodigious using this paradigm, that is, one in which subjects receive no manipulation prior to drug treatment. When subjects are chronically exposed to a mild stressor preceding antidepressant administration, larger effects are observed; presumably in this example, the drug is acting on an impaired reward system (29). Likewise, when the antidepressant effects are evaluated in animals that are undergoing cocaine withdrawal, a significant threshold-lowering effect is reported (26). Thus, our results may reflect an improvement in reward threshold that is near ceiling levels prior to treatment, such that substantial reductions in its value may not be realistic. There are human data to support this notion, that "normal" subjects are negligibly influenced by antidepressant treatment. For example, in one study (4) 6 weeks of drug administration failed to alter responses in controls on a number of well-known mood scales.

One mechanism for the antidepressant action on the reward substrate may be related to the proposed interaction between dopamine and serotonergic systems. There is evidence for an upregulation of mesolimbic dopamine receptors following chronic SSRI treatment (16), and it may be via this route that antidepressants modify reward signals.

The delay in therapeutic effect in clinical studies appears to coincide with several different physiological events. For example, it takes a few weeks for many of these compounds to reach a steady plasma concentration, although no correlation between efficacy and concentration has actually been established, particularly in the case of paroxetine (22,41).

A reduction in weight and food intake was observed initially in groups administered the higher doses of paroxetine (see Fig. 4). In particular, animals receiving the combination of stimulation and the 7.5 mg/kg dose showed a weight gain beginning at the third treatment session, and consequently, an increase in the percent efficiency of food utilization. Conversely, the paroxetine-treated animals alone exhibited a continuous weight loss, therefore giving rise to a very poor efficiency of food utilization throughout the drug treatment. Thus, it seems that stimulation counteracts the weight loss due to paroxetine. This SSRI, which increases postsynaptic serotonergic stimulation, is known to have an anorectic effect in humans by grossly reducing caloric intake (38). There is no clear explanation for the reversal in weight change and food intake by the animals receiving both paroxetine and stimulation, although alterations in the levels of peptides and immunological factors might be implicated. Cytokines, such factors, have been shown to decrease feeding by a direct action on the central nervous system (35). Furthermore, these factors have been implicated in sickness behavior and sickness-induced decreases in food-motivated behavior (21). Modulation of cytokine release by neurotransmitters has been shown (42); therefore, treatment with paroxetine, which increases serotonin levels in the brain, could potentially change cytokine release.

Intracranial stimulation could have altered neuropeptide Y levels in the brain, a substance shown to stimulate ingestive behavior (40). Interactions of this peptide with immunological factors could indirectly implicate neuropeptide Y in the attenuation of the initially observed anorexia and sickness behavior (39).

Another explanation for our finding of a seemingly protective effect of stimulation against the drug-induced anorexia may be related to alterations in endocrine and metabolic functions resulting from chronic stimulation. For example, it has been shown that LH stimulation raises the metabolic rate by as much as 40% (33). Finally, the efficient utilization of their food suggests that the animals receiving stimulation might be more capable of converting their energy intake into muscle mass, resulting in a net weight gain.

Because metabolism of paroxetine occurs mostly in liver, a visual inspection was done to verify its condition; we found obvious discoloration of the liver, particularly in animals administered the high dose. Bleeding attributed to the intake of paroxetine and fluoxetine in humans has been documented, and it is postulated that this bleeding is caused by drug-induced blood platelet dysfunction (2,32). A similar hypothesis may explain the presence of the hematomas that we observed in the animals receiving paroxetine; shortly after drug treatment was discontinued, the hematomas disappeared.

In conclusion, this study suggests that the rewarding value of stimulation increases with chronic administration of paroxetine in a delayed fashion. Furthermore, the time course of the drug-induced increase in reward value parallels that observed in humans. Some of the adverse drug effects, which are now being reported in the clinical literature, have been demonstrated in this animal model. It would be useful to further investigate the role of rewarding electrical stimulation in the modification of body weight induced by paroxetine, and whether this effect generalizes to other SSRIs.

ACKNOWLEDGEMENTS

This research was supported by a grant from the Natural Sciences and Engineering Council of Canada. The authors wish to thank SmithKline Beecham for the gift of paroxetine.

REFERENCES

1. Adler, L. A.; Angrist, B. M.: Paroxetine and akathisia. Biol. Psychiatry 37:336–337; 1995.
2. Aranth, J. A.; Lindberg, C.: Bleeding, a side effect of fluoxetine. Am. J. Psychiatry 149: 412; 1992.
3. Artigas, F.; Bel, N.; Casanovas, J. M.; Romero, L.: Adaptive changes of the serotonergic system after antidepressant treatments. In: Filippini, G. A.; Costa, C. V.; Bertazzo, A., eds. Recent advances in tryptophan research. New York: Plenum Press; 1996:51–59.
4. Barr, L. C.; Heninger, G. R.; Goodman, W.; Charney, D. S.; Price, L. H.: Effects of fluoxetine administration on mood response to tryptophan depletion in healthy subjects. Biol. Psychiatry 41:949–954; 1997.
5. Binks, S. M.; Murchie, J. K.; Greenwood, D. T.: A reward-reduction model of depression using self-stimulating rats: an appraisal. Pharmacol. Biochem. Behav. 10:441–443; 1979.
6. Blier, P.; De Montigny, C.; Chaput, Y.: Modifications of the serotonergic system by antidepressant treatments: Implication for the therapeutic response in major depression. J. Clin. Psychopharmacol. 7:24S–35S; 1987.
7. Boyer, W. F.; Feighner, J. P.: Side-effects of the selective serotonin re-uptake inhibitors. In: Feighner, J. P.; Boyer, W. F., eds. Selective serotonin re-uptake inhibitors. New York: John Wiley & Sons Ltd; 1991:133–152.
8. Burrows, G. D.; McIntyre, I.; Judd, F.; Norman, T. R.: Clinical effects of serotonin inhibitors in the treatment of depressive illness. J. Clin. Psychiatry (Suppl.) 49:18–22; 1988.
9. Collu, M.; Poggiu, A. S.; Devoto, P.; Serra, G.: Behavioral sensitization of mesolimbic dopamine D_2 receptors in chronic fluoxetine-treated rats. Eur. J. Pharmacol. 322:123–127; 1997.
10. Coppen, A.: The biochemistry of affective disorders. Br. J. Psychiatry 113:1237–1264; 1967.
11. Fibiger, H. C.; Phillips, A. G.: Increased intracranial self-stimulation in rats after long-term administration of desipramine. Science 214:683–685; 1981.
12. Frazer, A.: Pharmacology of antidepressants. J. Clin. Psychopharmacol. (Suppl.) 17:2S–18S; 1997.
13. Gallistel, C. R.: Self-stimulation in the rat: Quantitative characteristics of the reward pathway. J. Comp. Physiol. Psychol. 92:977–998; 1978.
14. Gardier, A. M.; Malagié, I.; Trillat, A. C.; Jacquot, C.; Artigas, F.: Role of 5-HT_{1A} autoreceptors in the machanism of action of serotoninergic antidepressant drugs: Recent findings from in vivo microdialysis studies. Fundam. Clin. Pharmacol. 10:16–27; 1996.
15. Hall, F. S.; Stellar, J. R.; Kelley, A. E.: Acute and chronic desipramine treatment effects on rewarding electrical stimulation of the lateral hypothalamus. Pharmacol. Biochem. Behav. 37:277–281; 1990.
16. Hammer, R. P., Jr.; Margulies, J. E.; Lynn, A. B.; Brady, L. S.: Chronic fluoxetine treatment upregulates dopamine receptors in the mesolimbic forebrain of the rat. Depression 1:82–87; 1993.
17. Harris, T. H.: Depression induced by Rauwolfia compounds. Am. J. Psychiatry 113:950–963; 1957.
18. Hjorth, S.; Auerbach, S. B.: 5-HT_{1A} autoreceptors and the mode of action of selective serotonin reuptake inhibitors (SSRI). Behav. Brain Res. 73:281–283; 1996.
19. Howell, D. C.: Statistical methods for psychology, 3rd ed.. Belmont: Duxbury Press; 1992.
20. Julien, R. M.: A primer of drug action: A concise, nontechnical guide to the actions, uses, and side effects of psychoactive drugs, 8th ed. New York: W. H. Freeman and Company; 1998.
21. Kent, S.; Bret-Dibat, J. L.; Kelley, K. W.; Dantzer, R.: Mechanisms of sickness-induced decreases in food-motivated behavior. Neurosci. Biobehav. Rev. 20:171–175; 1996.
22. Kuhs, H.; Schlake, H.-P.; Rolf, L. H.; Rudolf, G. A.: Relationship between parameters of serotonin transport and antidepressant plasma levels or therapeutic response in depressive patients treated with paroxetine and amitriptyline. Acta Psychiatr. Scand. 85:364–369; 1992.
23. Lane, R.; Baldwin, D.; Preskhorn, S.: The SSRIs: Advantages, disadvantages and differences. J. Psychopharmacol. (Suppl.) 9:163–178; 1995.
24. Lee, K.; Kornetsky, C.: Acute and chronic fluoxetine treatment decreases the sensitivity of rats to rewarding brain stimulation. Pharmacol. Biochem. Behav. 60:539–544; 1998.
25. Maes, M.; Meltzer, H. Y.: The serotonin hypothesis of major depression. In: Bloom, F. E.; Kupfer, D. J., eds. Psychopharmacology: The fourth generation of progress. New York: Raven Press; 1995:933–944.
26. Markou, A.; Hauger, R. L.; Koob, G. F.: Desmethylimipramine attenuates cocaine withdrawal in rats. Psychopharmacology (Berlin) 109:305–314; 1992.
27. McCarter, B. D.; Kokkinidis, L.: The effects of long-term administration of antidepressant drugs on intracranial self-stimulation responding in rats. Pharmacol. Biochem. Behav. 31:243–247; 1988.
28. Mobbs, C. V.; Rothfeld, J. M.; Saluja, R.; Pfaff, D. W.: Phorbol esters and forskolin infused into midbrain central gray facilitate lordosis. Pharmacol. Biochem. Behav. 34:665–667; 1989.
29. Moreau, J. L.; Jenck, F.; Martin, J. R.; Mortas, P.; Haefely, W. E.: Antidepressant treatment prevents chronic unpredictable mild stress-induced anhedonia as assessed by ventral tegmentum self-stimulation behavior in rats. Eur. Neuropsychopharmacol. 2:43–49; 1992.
30. Mundl, W. J.: A constant-current stimulator. Physiol. Behav. 24:991–993; 1980.
31. Nemeroff, C. B.: Paroxetine: An overview of the efficacy and safety of a new selective reuptake inhibitor in the treatment of depression. J. Clin. Psychopharmacol. 13(Suppl. 2):10S–17S; 1993.
32. Ottervanger, J. P.; Stricker, B. H.; Huls, J.; Weeda, J. N.: Bleeding attributed to the intake of paroxetine. Am. J. Psychiatry 151:781–782; 1994.
33. Pawson, P. A.; Preston, E.; Haas, N.; Foster, D. O.: Hypothalamic sites where electrical stimulation increases metabolic rate in the rat. Soc. Neurosci. Abstr. 13:1163; 1987.
34. Paxinos, G.; Watson, C.: The rat brain in stereotaxic coordinates, 2nd ed. San Diego, CA: Academic Press; 1986.
35. Plata-Salaman, C. R.; Oomura, Y.; Kai, Y.: Tumor necrosis factor and interleukin-1 beta: Suppresion of food intake by direct action on the central nervous system. Brain Res. 448:106–114; 1988.
36. Sachar, E. J.; Baron, M.: The biology of affective disorders. Ann. Rev. Neurosci. 2:505–518; 1979.
37. Schildkraut, J. J.: The catecholamine hypothesis of affective disorders: A review of supporting evidence. Am. J. Psychiatry 122:509–520; 1965.
38. Simansky, K. J.: Serotonergic control of the organization of feeding and satiety. Behav. Brain Res. 73:37–42; 1996.
39. Sonti, G.; Ilyin, S. E.; Plata-Salaman, C. R.: Neuropeptide Y blocks and reverses interleukin-1β-induced anorexia in rats. Peptides 17:517–520; 1996.
40. Stanley, B. G.; Chin, A. S.; Leibowitz, S. F.: Feeding and drinking elicited by central injection of neuropeptide Y: Evidence for a hypothalamic site(s) of action. Brain Res. Bull. 14:521–524; 1985.
41. Tasker, T. C. G.; Kaye, C. M.; Zussman, B. D.; Link, C. G.: Paroxetine plasma levels: Lack of correlation with efficacy or adverse events. Acta Psychiatr. Scand. (Suppl.) 80:152–155; 1989.
42. Tringali, G.; Mirtella, A.; Mancuso, C.; Guerriero, G.; Preziosi, P.; Navarra, P.: The release of immunoreactive interleukin-1β from rat hypothalamic explants is modulated by neurotransmitters and corticotropin-releasing hormone. Pharmacol. Res. 36: 269–273; 1997.
43. Valentino, D. A.; Riccitelli, A. J.; Dufresne, R. L.: Chronic DMI reduces thresholds for brain stimulation in the rat. Pharmacol. Biochem. Behav. 39:1–4; 1991.
44. Zhu, X.-O.; McNaughton, N.: The interaction of serotonin depletion with anxiolytics and antidepressants on reticular-elicited hippocampal RSA. Neuropharmacology 33:1597–1605; 1994.