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Isatin inhibits food intake in mice

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Abstract

Isatin (2,3-dioxindole) is an endogenous compound which is distributed throughout the central nervous system. The studies reported here demonstrate that isatin decreased food intake in food deprived TAC (SW) male mice 12–16 weeks of age. Isatin was more effective at decreasing food intake when the mice had to work harder to obtain food. Isatin also decreased sucrose, milk and water intake. When hunger was reduced by prefeeding milk to the mice, isatin was more effective at decreasing food intake. Isatin did not alter spontaneous activity in an openfield. Behaviors observed in the home cage indicated that mice which received isatin approached the food more often without eating than the controls. Movement in the home cage was significantly reduced in mice receiving isatin. Drinking, grooming and resting were not significantly affected by administration of isatin. These studies suggest that isatin may be an endogenous modulator of food intake.

Keywords: Appetite; Drinking; Food intake; Isatin; Motivation; 5-HT (5-hydroxytryptamine, serotonin); Tubulin; (Mouse)

1. Introduction

Tribulin is an endogenous monoamine oxidase (MAO) inhibitor (Glover et al., 1980). Isatin (2,3-dioxoindole) is a major component of tribulin which is a selective inhibitor of monoamine oxidase B (Glover et al., 1988). Isatin is distributed throughout the brain and peripheral tissues (Watkins et al., 1990) and has been demonstrated to be anxiogenic in animal models (Bhattacharya and Acharya, 1993). Isatin, when administered to rats in vivo increases brain serotonin levels (Kumar et al., 1994). Recently, Brewerton et al. (1995) found that cerebrospinal fluid levels of isatin were increased in patients with bulimia nervosa.

Appetite regulation is a complex process involving both central nervous system neurotransmitter and peripheral factors (Blundell, 1991; Morley, 1987). Numerous studies have demonstrated a role for serotonin in appetite regulation (Blundell, 1992; Leibowitz et al., 1990). Serotonin decreases food intake through a direct effect within the medial hypothalamus. In view of the findings that isatin increases serotonin levels (Kumar et al., 1994) and that isatin levels are altered in bulimia (Brewerton et al., 1995), it appeared reasonable to investigate its effects on food intake. The studies reported here provide evidence that isatin decreases food and water intake in mice.

2. Materials and methods

2.1. Subjects

Food intake was studied in TAC(SW) male mice, 12–16 weeks of age, obtained from Taconic Farms (Germantown, NY, USA). They were housed in single cages with a 12 : 12 light-dark cycle (lights on at 06:00 h) with the room temperature varying between 20 and 24°C. Water and food (Richmond Laboratory Rodent Diet 5001, formerly Purina Rodent Chow 5001) were available ad libitum, except where noted. All mice were adapted to the laboratory environment for at least 2 weeks before testing began. Food intake was studied between 07:00 to 09:00 h.

2.2. Isatin preparation

Isatin was purchased from Sigma Chemical Company (St Louis, MO, USA). Isatin was prepared fresh daily as dilute solutions form deposits on the side of injection vials

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if allowed to settle for more than a few hours. Weighed isatin powder was wetted with 70 μl of absolute ethanol, diluted with half saline and heated and agitated with a heat-stirrer (VWR Model 220) until the isatin was dissolved. The isatin at 5 mg/ml (50 mg/kg) did not clear and remained as a suspension. The vehicle contained 70 μl of absolute ethanol in 10 ml of distilled water and 10 ml of saline. All solutions were kept warm. We injected vehicle or isatin solutions intraperitoneally. The effect of isatin on food intake was measured over a 30 min period following its administration, except in experiment 1 where food intake was determined after 30 and 60 min following vehicle or isatin administration.

2.3. Measurement of food pellet, sucrose, milk or water consumption

Food pellet consumption was measured by placing a weighed pellet in the bottom of the animal's cage or by placing several weighed pellets in the hopper and determining the difference in food pellet weight after the test. It is more difficult for mice to eat the food pellets in the hopper and, therefore, we used this as a test of how an increase in effort to get the food affected the ability to modulate inhibition of food intake. In experiment 1, we placed a weighed food pellet into the cage and weighed the pellet again 30 min and 60 min after vehicle or isatin administration. In experiments 2, 3 and 7 approximately 50 g of food was placed into the cage lid food hopper and was weighed again 30 min after vehicle or isatin administration.

Rodents do not readily consume novel foods even if they are eventually preferred. The mice were given 40 ml of a 15% sucrose solution or milk (canned evaporated milk diluted with two parts water) on Monday, Wednesday and Friday in place of food and water the week prior to the study. Subjects not consuming at least 80% of the available solution were discarded prior to the study. Sucrose or milk were provided during habituation and during the test in 50 ml graduated centrifuge tubes fitted with a rubber stopper and a dripless drinking spout. The tubes were inserted through the bars of the wire cage lid.

When water consumption was measured, mice were water, but not food, deprived overnight as in the food pellet feeding studies. In the morning, vehicle or isatin (25 mg/kg, i.p.) was administered. Immediately after drug administration, food was removed from the cage lid and replaced with weighed centrifuge tubes filled with tap water. Total fluid consumption was determined 30 min later by weighing the centrifuge tubes and calculating the difference.

2.4. Observed behaviors in the home cage

Beginning 1 min after receiving isatin (25 mg/kg, i.p.) or vehicle injection, mice were observed once each minute and their behavior was rated as: moving, resting, grooming, drinking, approaching the food hopper and eating, approaching the food hopper and *not* eating. Moving included any preambulation not related to other activities. Resting was any type of inactivity. In pilot studies, isatin injected mice were observed to sit under the food hopper or stand up touching or moving the food pellets in the hopper, but the mice did not actually gnaw or chew the food pellets. This type of behavior, indicative of reduced interest in eating, relative to those that ate the pellets, was scored as approaching food but not eating.

2.5. Monitoring general activity

To determine if inhibition of food intake might have been due to a general malaise, we determined the effect of vehicle or isatin (25 mg/kg) administration on general activity in a round openfield using an automated tracking system (San Diego Instruments, PolyTrak). As in the feeding studies, mice were deprived of food overnight. With 10 mice per group, one group received 25 mg/kg of isatin and the other vehicle. Starting immediately after the injection, activity was monitored for 30 min. The measure of activity was centimeters traveled.

2.6. Statistical evaluation

All results are expressed as means and S.E.M. For studies involving only two groups, statistical difference between the means was tested using Student's *t*-test. In other designs, the statistical significance was determined by an analysis of variance (ANOVA). Dunnett's *t*-test was used to determine if the differences between the mean of the control group differed from the experimental groups in a one-way ANOVA. In the case of ANOVAs with two or more factors, Tukey's *t*-test was used to determine if means differed significantly.

3. Results

3.1. Experiment 1: effect of isatin on food pellet intake with the pellet in the bottom of the cage

Mice were food, but not water, deprived for 17 h prior to this study. In this experiment, mice received 5, 10, 25, or 50 mg/kg of isatin or vehicle. There were 14–15 mice per group. The amount of food pellet consumed was measured over a 0–30 min and 31–60 min test periods. The food consumed was analyzed by a two-way ANOVA (drug × time of testing) with repeated measures over time of testing. The results indicated that the main effect of the dose of isatin was significant, $F(4,138) = 3.93$, $P < 0.01$, as was the main effect of time of testing (first versus second 30 min periods), $F(1,28) = 366.81$, $P < 0.001$. The interaction of these factor was also significant,

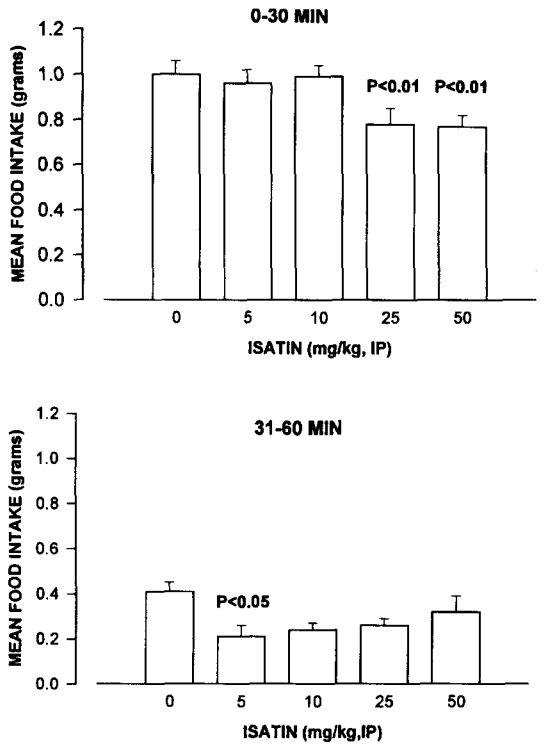

Fig. 1. Effect of isatin on food intake as a function of dose and time food intake was measured. Food intake was measured after receiving the indicated injections from 0 to 30 min (Top) and from 31 to 60 min (Bottom). The bars represent the means and standard error of the means.

$F(4,128) = 3.46$ $P < 0.025$. The mean food intake for groups receiving 25 or 50 mg/kg differed from the vehicle control at $P < 0.01$ by Tukey's t-test during the 0–30 min test period (Fig. 1). During the next 30 min only the mean of the group receiving 5 mg/kg differed significantly from the mean of the vehicle control at $P < 0.05$.

3.2. Experiment 2: effect of isatin on food intake from the hopper

Mice were food, but not water, deprived for 17 h prior to this study. In this experiment, mice received 25 mg/kg of isatin or vehicle. There were 10 mice per group. The amount of food pellet consumed over a 30 min test period was measured. Student's t-test indicated that the mean and S.E.M. food intake of the group treated with isatin (0.47 ± 0.07 g) was significantly smaller than that of the vehicle control (0.85 ± 0.07 g), $t = 3.50$, $P < 0.005$. The isatin group in this experiment showed a 47% suppression of food intake relative to the vehicle control compared to 22% suppression of food intake in experiment 1 where the food pellet was in the bottom of the cage.

3.3. Experiment 3: a comparison of the effect of isatin on food intake when food is on the floor verus in the food hopper

Experiments 1 and 2 suggest that isatin was more effective at suppressing food intake when food was made less readily available to the mice by placing it in the food hopper. However, because baseline food intake varies across days, we tested the effect of saline and 25 mg/kg of isatin on food intake when food pellets were placed in the food hopper or a single pellet was placed on the floor of the cage. The conditions were similar to those in experiment 1 and 2.

The results of a two-way ANOVA run on grams food intake indicated that both the main effects of the dose of isatin administered, $F(1,56) = 13.52$, and the location of the food, $F(1,56) = 16.84$, were significant at $P < 0.001$. The interaction was not significant. Whether food was in the hopper or on the floor of the cage, the mean of the saline injected groups was significantly higher than the mean of the isatin injected groups at $P < 0.05$ using Dunnett's t-tests. However, the percentage food suppression was greater when food was located in the hopper (Fig. 2).

3.4. Experiment 4: the effect of the duration of time of pretreatment with isatin on its ability to inhibit food suppression

The purpose of this study was to obtain an estimate of how long isatin could be injected before it failed to decrease food intake. Mice were food, but not water, deprived for 17 h prior to this study. In this experiment, mice received 25 mg/kg of isatin or vehicle and 0, 30, 60 or 90 min *later* food was placed in the food hopper in the cage lid. There were 14 mice per group. The amount of food pellet consumed over a 30 min test period was measured.

Food intake was analyzed by a two-way ANOVA (drug by time). The results indicated that the main effect of drug,

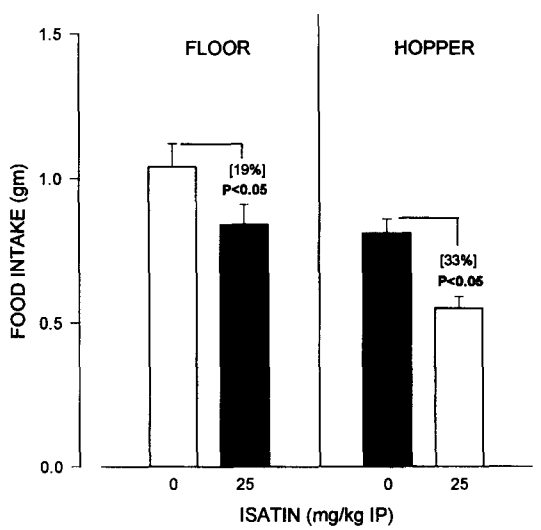

Fig. 2. Effect of isatin on food intake as a function of where the food is located. The bars represent the means and standard error of the means. The value in brackets is the percent suppression in food intake relative to the vehicle control (0 mg/kg).

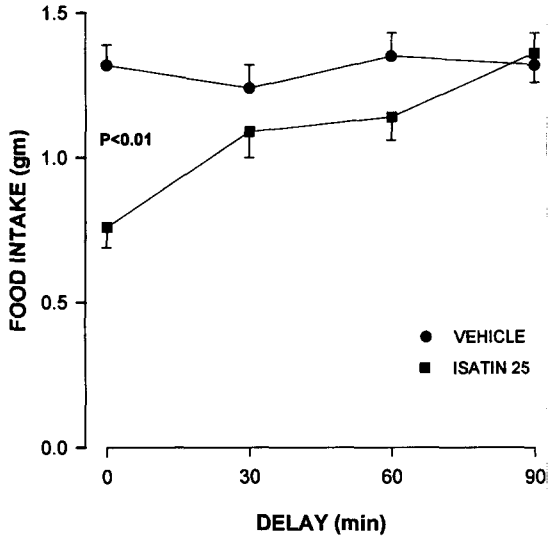

Fig. 3. The effect of the duration of time since isatin administration on its ability to inhibit food intake. The delay on the *X*-axis indicates the period of time between administration of vehicle or isatin and the time at which the test of food consumption began. Food was not placed in the food hopper until the end of the delay period. The bars represent the means and standard error of the means.

$F(1,104) = 15.83$, $P < 0.001$, time, $F(3, 104) = 5.02$, $P < 0.005$ and the interaction, $F(3,104) = 4.92$, $P < 0.005$, were significant. Fig. 3 shows that the main effect of drug was that isatin resulted in a decrease in food consumption. The means of the vehicle and isatin treated groups differed significantly when food was available immediately after the injection (0 min) at $P < 0.01$. The main effect of time was due to the decreasing effect of isatin on food intake as the duration of time prior to giving food increased. The delay period did not effect food intake of the controls. The interaction was significant because the duration of the delay prior to providing food had an effect on mice treated with isatin but did not have an effect on mice treated with the vehicle.

3.5. Experiment 5: effect of isatin on sucrose consumption

In this study, mice were habituated to a novel but preferred food, sucrose solution, as described above. Mice were food and water deprived for 17 h prior to this study. Mice received 25 mg/kg of isatin or vehicle with 15 mice per group. The amount of sucrose consumed over a 30 min test period was measured. Mice given saline consumed 2.77 ± 0.16 g of sucrose solution compared to 1.77 ± 0.15 g for those given isatin. The difference in the means was significant at $P < 0.002$ by a two-tailed Student's *t*-test ($t = 4.56$).

3.6. Experiment 6: effect of isatin on consumption of milk in prefed and non-prefed mice

The motivation to eat can be manipulated by changing hunger. In this study, mice were prefed milk to determine if reducing hunger would increase food suppression by isatin. In addition, we manipulated hunger by using 15 or 30 min delays, to allow the stomach to partially empty, between the end of prefeeding and the testing of isatin's effect on milk consumption.

Mice were food and water deprived for 17 h prior to this study. Half the mice were allowed to consume the milk for 15 min to reduce their appetite. These groups were further divided into those that were administered isatin or vehicle either 15 or 30 min after consuming the milk. Mice received 25 mg/kg of isatin or vehicle. There were a total of 8 groups with 15 mice per group (Fig. 3). The amount of milk consumed over a 30 min test period was measured.

Milk consumption was analyzed by a three-way ANOVA (drug dose × prefed status × delay prior to testing). The ANOVA indicated the main effects of drug and whether mice were prefed or not prefed had significant effects at $P < 0.001$ (Table 1). The main effect of the interval between prefeeding and testing was significant at $P < 0.025$. Only the interaction between prefed status and interval between prefeeding and testing was significant at $P < 0.001$. As Fig. 3 indicates the main effect of drug was due to an overall reduced consumption of milk by groups receiving isatin compared to vehicle. The main effect of prefeeding status was that three of the four prefed groups consumed less than non-prefed groups. The significant main effect of the interval between prefeeding and testing was due to an overall reduced consumption of milk by those with a 15 min delay compared to a 30 min delay. However, the effect was clearly dominated by the 15 min

Table 1
Summary of the three-way ANOVA for experiment 5; the effect of isatin on milk consumption

Source	df	SS	MS	*F*	*P* <
Drug dose	1	29.44	29.44	40.98	0.001
Interval	1	4.56	4.56	6.35	0.025
Prefed status	1	18.79	18.79	26.16	0.001
Drug × interval	1	0.002	0.002	0.003	
Interval × prefeeding	1	8.41	8.41	11.70	0.001
Drug × prefeeding	1	1.21	1.21	1.68	
Drug × interval × prefeeding	1	0.46	0.46	0.65	
Error	111	79.75	0.72		
Total	118	142.62			

delay in the prefed groups, which gives rise to the significant interaction of prefeeding and the delay interval before testing, since prefed mice with a 15 min delay consumed less that those with a 30 min delay or with no prefeeding (Fig. 4).

3.7. Experiment 7: the effect of isatin on water consumption

Water consumption in isatin-treated mice was depressed by 32% compared to the vehicle controls over a 30 min test period. The mean and S.E.M. for water intake was 1.81 ± 0.07 g for the vehicle and 1.23 ± 0.07 g for the isatin treated group. The difference was significant by a two-tailed Student's t-test at $P < 0.002$ ($t = 6.02$).

3.8. Experiment 8: the effect of isatin on behaviors in the home cage

Over a 30 min test period, isatin-treated mice were observed to show reduced incidence of eating, drinking and moving, as well as, increased approaches to the food without eating and resting relative to the behavior of the vehicle control (Fig. 5). Of these changes, only the means for moving and approaching but not eating the food yielded significant differences between vehicle and isatin (25 mg/kg, i.p.) treated mice. The means differed for both behaviors at $P < 0.002$ by a two-tailed Student's t-test ($t = 3.59$ for moving; $t = 3.45$ for approach but not eat). In this study, actual food intake was also measured. The mean food intake for the group receiving the vehicle was 1.02 ± 0.05 g while the isatin group showed a reduction in consumption with 0.69 ± 0.11 g; the difference was significant at $P < 0.002$ ($t = 3.47$).

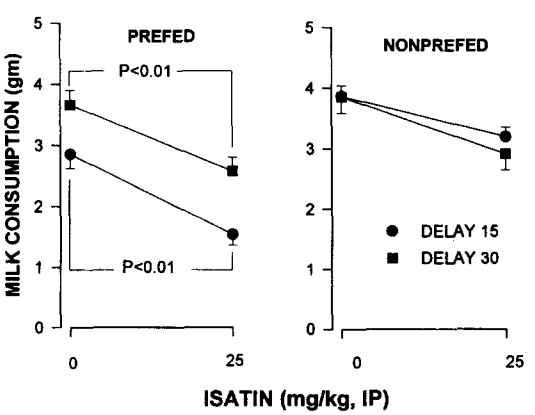

Fig. 4. The effect of isatin, prefeeding and the delay between prefeeding and drug administation on milk consumption. Mice were prefed milk to reduce their hunger. The 15 and 30 min delay periods refer to the duration of time between the end of the prefeeding and the administration of vehicle or isatin. The test of milk consumption occurred immediately after drug or saline administration. Consumption was measured for a 30 min period. The two delay periods were used to test the effect of different durations of time that the stomach had to empty on milk comsumption. The bars represent the means and standard error of the means.

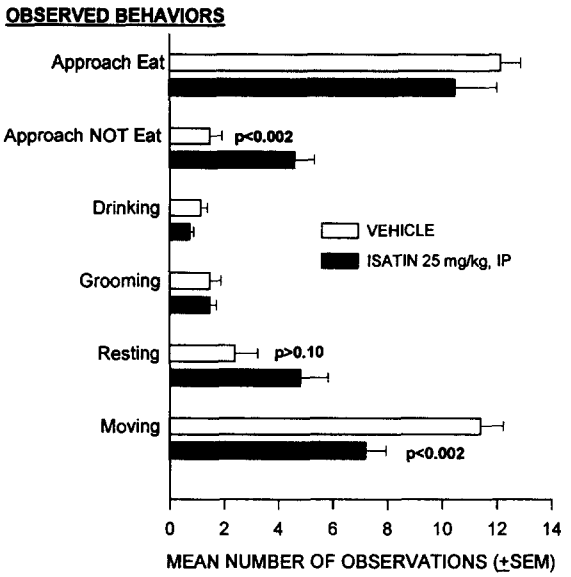

Fig. 5. The effect of isatin on observed behaviors in the home cage.

3.9. Experiment 9: the effect of isatin on activity

To determine if inhibition of food intake might have been due to a general malaise, we determined the effect of vehicle or isatin (25 mg/kg) administration on general activity. The mean and standard error for distance traveled was 3927 ± 177 cm for the vehicle and 4003 ± 137 cm for the isatin group. The means were not significantly different (Student's t-test, $t = 0.32$).

4. Discussion

The studies reported here demonstrate that isatin decreased food intake after peripheral administration in mice. Isatin decreased consumption of food pellet, sucrose, milk and water. Previously, our group (Billington et al., 1983; Flood et al., 1990) and others (Bellinger and Mendel, 1985) have argued that true satiating substances should be less effective when the animal has an increased motivation to eat (e.g. satiating substances such as cholecystokinin are less effective as the period of food deprivation is increased) and more effective when partially satiated or the effort to obtain food is increased such as requiring the mice to lever press for food (Flood et al., 1990). The studies reported here demonstrated that isatin behaved as might be expected of a true satiating substance.

In experiment 3, food was either placed in the food hopper or on the floor of the cage. The saline controls with food available on the floor ate 22% more than the saline controls with food in the hopper indicating that food was more readily eaten when it was on the floor of cage where it was easier to eat. As indicated above, a satiating agent should be less effective when there is less effort required to obtain the food. The percentage suppression of food

intake by isatin was lower when food was on the floor, 19%, than when it was in the hopper, 32%. A similar trend in percentage suppression by isatin was also observed in experiment 1 with food on the floor, 22% suppression and experiment 2 with food in the hopper, 47% suppression. Thus a small increase in effort to eat enhanced the suppression of food intake by isatin relative to the saline-treated mice.

In experiment 6, we manipulated hunger by giving or not giving milk prior to testing the effect of isatin on milk intake. Reduced hunger should enhance the effect of isatin by reducing the motivation to eat. Overall, isatin suppressed feeding among mice prefed milk but was without significant effect in the hungrier mice that were not prefed (Fig. 4). In addition, we waited either 15 or 30 min after prefeeding the mice milk before administering saline or isatin. As the delay increases, the stomach should empty and hunger increase. Isatin should be more effective at suppressing feeding after a 15 min delay than after a 30 min day. Among the prefed mice, the percentage suppression of milk intake by isatin was greater at 15 min (46%) than at 30 min (29.5%). Thus, when hunger was decreased by prefeeding, then isatin was more effective at suppressing food intake and when hunger was increased, due to the stomach contents decreasing, then isatin was less effective at suppressing food intake.

Isatin significantly suppressed sucrose consumption in experiment 5. However, isatin did not significantly suppress milk consumption in mice not prefed with milk in experiment 6. The differential effect of isatin with these two food substances probably has to do with their respective mechanisms of inhibiting food intake and the speed with which they do it. Sucrose passes through the stomach quickly and is absorbed from the intestine rapidly. The result is a rapid increase in serum glucose that inhibits feeding. Milk turns to a semi-solid in the stomach resulting in gastric distension which over time inhibits further food intake. The difference in time course is reflected in how long it takes to inhibit feeding in mice. Mice will consume sucrose almost constantly for about 15 min and will not resume feeding for at least 60 min. Mice will consume milk for about 30 min and will resume feeding again after another 30 min a time at which some gastric emptying has occurred. In the study involving sucrose, its rapid ability to be absorbed and to reduce hunger would facilitate the effect of isatin. In the milk study, satiation due to gastric distension takes about 30 min which is probably why isatin suppressed food intake in mice that were prefed but did not suppress feeding in non-prefed mice.

In experiment 4, we administered saline or isatin then waited for different time intervals before giving the mice food so that we could determine how long isatin could be in the animal's system before it failed to significantly suppress feeding. The results of experiment 4 indicated that food intake was significantly suppressed when food was given immediately, but not 30 min or longer, after isatin administration. Bhattacharya and Acharya (1993) reported that 20 mg/kg of isatin given to rats increased the concentration of serotonin and its metabolites up to at least 60 min after administration, with peak effects obtained 30 min after administration. The discrepancy between our feeding study and their biochemistry may, in part, be due to the biochemistry being done in rats, i.e. a species difference. In comparing the effect of isatin at 10 mg/kg which weakly inhibit feeding with that of 20 mg/kg, at 60 min the 10 mg/kg dose increased serotonin in rat brain by 33%, while the 20 mg/kg dose increased serotonin by 96%. The threshold for increased serotonin to effect behavior is between 33% and 96%. Mice have a higher metabolic rate than rats and the effect of isatin on serotonin might be more rapid but shorter lasting. In addition, altered serotonin levels are only one component of neurochemical control of feeding and a correlation of one to one should not be expected.

Numerous neurotransmitters modulate short-term food intake (Blundell, 1991; Morley, 1987). Isatin is an endogenous substance which is localized in the brain in a number of areas known to be involved in the regulation of food intake (Watkins et al., 1990). Bhattacharya and Acharya (1993) report that isatin given to rats, increased the concentration of serotonin in the brain with a greatest effect in the hypothalamus and midbrain. The mechanism by which isatin decreases food intake may be related to its ability to increase serotonin (Kumar et al., 1994). Serotoninergic agonists suppress feeding (Leibowitz et al., 1990). Chronic administration of drugs that increase serotonin decreased food intake and weight in mice (Morley and Flood, 1987) and humans (Weintraub et al., 1992). Further studies will be required to determine whether isatin produces its anorectic effect only by increasing brain serotonin levels or through some of its other effects such as its ability to inhibit MAO-B activity, brain acetylcholinesterase or sodium, potassium-adenosine triphosphate (Kumar et al., 1994).

The significant suppression of water intake by isatin was the only data suggesting isatin might inhibit food intake by causing a general malaise. Activity outside the home cage was not significantly effected as one might expect if isatin were making the mice 'ill'. The observational study indicated some interest in the food as the mice approached the food hopper and were observed to manipulate the food pellets but they did not actually eat. If the mice were made ill or they were tranquilized we would expect that they would not even approach the food.

Tribulin is an endogenous MAO inhibitor (Glover et al., 1980). Isatin is a component of tribulin (Glover et al., 1988) with a relatively specific inhibitory action of MAO-B. Inhibition of MAO-B can increase dopamine and serotonin levels. Bhattacharya and Acharya (1993) report that administration of 20 mg/kg of isatin in rats increased serotonin concentration in the hypothalamus by 96% which is an area of the brain important in regulation of food

intake (Leibowitz et al., 1990). Isatin acts as an anxiogenic in a variety of animal models (Bhattacharya and Acharya, 1993) and a variety of stressors produce anorexia (Morley et al., 1983). Isatin does not account for all the activity ascribed to tribulin (Sandler, 1982) and its ability to suppress food intake may be related to effects on dopamine or other actions of isatin. Isatin may prove to be an endogenous substance involved in feeding and the pathogenenis of stress-induced anorexia.

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References

Bellinger, L.L. and V.E. Mendel, 1985, The effect of intracerebroventricularly infused satietin on conditioned taste aversion and feeding in rats fasted different lengths, Pharmacol. Biochem. Behav. 23, 559.

Bhattacharya, S.K. and S.B. Acharya, 1993, Further investigations on the anxiogenic effects of isatin, Biogenic Amines 9, 453.

Billington, C.J., A.S. Levine and J.E. Morley, 1983, Are peptides truly satiety agents? A method of testing for neurohumoral satiety effects, Am. J. Physiol. 245, R920.

Blundell, J.E., 1991, Pharmacological approaches to appetite suppression, Trends Pharmacol. Sci. 12, 147.

Blundell, J.E., 1992, Serotonin and the biology of feeding, Am. J. Clin. Nutr. 55, 155S.

Brewerton, T.D., J.J. Zealberg, R.B. Lydiard, V. Glover, M. Sandler and J.C. Ballenger, 1995, CSF isatin is elevated in bulimia nervosa, Biol. Psychiat 37, 481.

Flood, J.F., A.J. Silver and J.E. Morley, 1990, Do peptide-induced changes in feeding occur because of changes in motivation to eat?, Peptides 11, 265.

Glover, V., M.A. Reveley and M. Sandler, 1980, A monoamine oxidase inhibitor in human urine, Biochem. Pharmacol. 29, 467.

Glover, V., J.M. Halket, P.J. Watkins, A. Clow, B.L. Goodwin and M. Sandler, 1988, Isatin identity with the purified endogenous monoamine oxidase inhibitor tribulin, J. Neurochem. 51, 656.

Kumar, R., R.C. Bansal and A. Mahmood, 1994, In vivo effects of isatin on certain enzymes, lipids and serotonergic system of the rat brain, Indian J. Med. Res. 100, 246.

Leibowitz, S.F., G.F. Weiss and J.S. Suh, 1990, Medial hypothalamic nuclei mediate serotonin's inhibitory effect on feeding behaviors, Pharmacol. Biochem. Behav. 37, 735.

Morley, J.E., 1987, Neuropeptide regulation of appetite and weight, Endocrine Rev. 8, 256.

Morley, J.E. and J.F. Flood, 1987, An investigation of tolerance to the actions of leptogenic and anorexigenic drugs in mice, Life Sci. 41, 2157.

Morley, J.E., A.S. Levine and N.E. Rowland, 1983, Stress induced eating, Life Sci. 32, 2169.

Sandler, M., 1982, The emergence of tribulin, Trends Pharmacol. Sci. 3, 471.

Watkins, P., A. Clow, V. Glover, J. Halket, A. Przyborowska and M. Sandler, 1990, Isatin, regional distribution in rat brain and tissues, Neurochem. Int. 17, 321.

Weintraub, M., P.R. Sundaresan, M. Madan, B. Schuster, A. Balder, L. Lasagna and C. Cox, 1992, Long-term weight control study I (weeks 0 to 34). The enhancement of behavior modification, caloric restriction, and exercise by fenfluramine plus phentermine versus placebo, Clin. Pharmacol. Ther. 51, 586.