

Intraaccumbens baclofen selectively enhances feeding behavior in the rat

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Received 17 May 1999; received in revised form 3 September 1999; accepted 7 October 1999

Abstract

Intraaccumbens infusions of the GABA_B agonist baclofen are known to stimulate food intake in the rat. The aim of the present study was to evaluate the effects of baclofen infusion on nonfood-related chewing and on the consumption of a palatable fluid. Rats were bilaterally infused with baclofen (188 ng in 1 μ L) or saline, and tested in a situation in which food was available in one or two locations and wood blocks might also be present. Baclofen-infused animals showed no enhancement of chewing directed at the wood blocks, but showed increased food consumption regardless of food location. In a second, separate test we recorded the microstructural parameters for drinking of a palatable glucose/saccharin mixture. Baclofen infusion had no effect on overall intake, although bout size was reduced and the number of bouts was increased. These data confirm that baclofen-stimulated food intake following accumbens infusion is a robust and substantial phenomenon that appears to be selective to solid food. It is likely to result from relatively direct activation of neural circuits for feeding, rather than an indirect facilitation consequent upon changes in taste processings, as has been suggested for some other examples of drug-induced hyperphagia. © 2000 Elsevier Science Inc. All rights reserved.

Keywords: Baclofen; Feeding behaviour; Nucleus accumbens; Drinking microstructure; Chewing; Stereotypy; Palatability; Hyperphagia

1. Introduction

Drug-induced hyperphagia is an important phenomenon in the analysis of the neurochemical modulation of ingestive behaviour. For example, enhancement of food intake following administration of both serotonin and CCK antagonists has been taken as strong evidence supporting involvement of these neurotransmitters in the endogenous control of ingestive behavior [1]. Drug-induced increases in food intake are less subject to the problems of interpretation that arise with drug-induced reductions in food intake in which nonselective changes in arousal or the induction of sickness may play a role. Although the induction of a stereotyped chewing response that is directed against any appropriate object has been regarded as a potential hypothesis to explain 8-OH-DPAT-induced food intake, the simultaneous presentation of food (e.g., chow pellets) and nonfood items (e.g., wooden blocks of similar size) in 8-OH-DPAT-treated animals leads to a behavioral response directed almost solely to food, suggesting a selective enhancement of ingestive behaviour [2].

A related issue is the extent to which drug-induced hy-

perphagia affects intake of both solid and liquid food, and the investigation of this may help to clarify the means by which the drug manipulation leads to a change in overt behavior. There are clear distinctions to be drawn between the effects of pharmacological manipulation of different neurotransmitter systems. For example, benzodiazepines, such as the partial agonist bretazenil, produce very reliable increases in the intake of both solid and liquid food [3,4] with similar dose dependencies. Systemic administration of opiates is associated with increased solid food consumption and also enhanced intake of both sucrose and saccharin solutions, although these effects vary with food deprivation and time of day [5]. Central action of opioid peptides, especially ligands at the mu and delta receptors, is also associated with enhanced food intake [6], sucrose drinking [7], and saccharin consumption [8]. In contrast, enhancement of intake of a palatable liquid has been difficult to establish following treatment with 8-OH-DPAT, even at doses that increase solid food intake, although it can be achieved following presatiation [9,10].

The GABA_B agonist baclofen is known to stimulate solid food intake following systemic [11], intraraphe [12], or intraaccumbens [13] administration. The effect of intraaccumbens administration appears to be an especially robust effect, producing 200–300% increases in intake during a 2-h test session [13]. Here we investigate the behavioral specificity of this effect in the context of solid food as well as

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whether there are effects on the ingestion of a palatable, calorie-containing solution in nonfood-deprived rats. Two feeding manipulations were used: the first provided a simple measure of enhanced consumption, and the second provided access to food in one or two possible locations. Moreover, to separate food consumption from stereotyped chewing we included an additional variable in the second manipulation, where wooden blocks with similar physical characteristics to the food pellets were supplied in a semi-randomised design with the food. The drinking test provided a detailed description of the rat's ingestive patterns while consuming a highly palatable glucose/saccharin solution. Intake of this solution is strongly facilitated by the benzodiazepine partial agonist bretazenil [4] over the same dose range that produces an enhancement of the intake of solid food [3].

2. Materials and methods

2.1. Animals, surgery, and drugs

Male Lister hooded rats, bred at the University of Sussex, weighing 300–350 g at the start of the experiment, were individually housed in a solid-bottomed polyethylene cage (North Kent Plastics RB3). The animals were maintained on an ad lib diet of standard laboratory chow (Special Diet Services, Harlow) and tap water with a 12 h on:12 h off light–dark cycle: lights on at 0700 h. Holding rooms were maintained at a temperature of $21 \pm 1^\circ\text{C}$, and at a relative humidity of $50 \pm 10\%$. All experiments were authorised by the UK Animals (Scientific Procedures) Act, 1986.

At approximately 350 g body weight, the rats were implanted with permanent indwelling stainless steel cannulae. Anesthesia was induced using halothane (4%), nitrous oxide (0.5 L/min) and oxygen (0.5 L/min). The subjects were then transferred to a stereotaxic apparatus (Kopf) and halothane concentration adjusted to give a constant depth of anesthesia in the subsequent procedure. Twenty-three gauge stainless steel cannulae (Coopers Needleworks, Birmingham), 16 mm in length, were implanted bilaterally, aimed at a position 2.2 mm above the posterior nucleus accumbens shell; flat skull: AP 1.2 mm, lateral 1.5 mm relative to bregma, and ventral –6 mm relative to skull surface [14]. The cannulae were anchored to the skull using three 1.6-mm self-tapping stainless steel screws (Plastics One, Roanoke, VA) and acrylic dental cement (Simplex). Stainless steel obturators were used to occlude the cannulae. Drug infusions were made after two dummy injections, performed on successive days, during which the injector was lowered to its full depth and then retracted. All subjects were given one sham injection of sterile 0.9% saline (pH neutral) on the day before the first counterbalanced drug/vehicle tests in both the eating and drinking experiments. The infusion cannulae were 30-g stainless steel tubing cut with a stop 18.2 mm from one end made from epoxy adhesive. Prior to each of the feeding and drinking experiments, half the rats were infused with the

GABA_B agonist baclofen (Sigma) at a concentration of 188 ng (880 pM) per μL , the other half with 1 μL pH-adjusted 0.9% saline; at a rate of 0.5 μL per side, infused by hand over 90 s. The dose chosen had been shown to be highly effective in the initial report of this phenomenon [13].

2.2. Behavioral testing

Fifteen animals, in total, were tested; nine were initially tested in the drinking manipulation and then in the feeding manipulation: 1; the remainder were initially tested in feeding manipulation 2, and then in the drinking manipulation.

2.2.1. Feeding manipulation 1

Following intracerebral infusion, the subjects were immediately placed into a standard housing cage, identical to the home cage, with a Petri dish in the center of the floor containing a known weight of standard chow pellets. Both the suspended food hopper and the water bottle were of known weight. Intake was calculated by reweighing the food containers and water bottle following the test, after collecting and replacing any food spilt from the Petri dish.

2.2.2. Feeding manipulation 2

To test for possible gnawing stereotypies, the consumption of standard chow in a standard housing cage was compared to the consumption of equivalently sized and shaped softwood blocks. Using an ascending half Latin square design the rats were placed into one of three situations following infusion of either baclofen or pH adjusted saline. In the first test situation the cage contained a Petri dish with 10 standard chow pellets, a normal suspended food hopper full of standard chow, and a normal drinking bottle full of tap water. The second test situation contained a Petri dish with wooden blocks of the same size, color, and shape to the food pellets, and in the third test situation, the Petri dish was empty. The rats were bilaterally infused into the nucleus accumbens and immediately placed in the cage. Consumption from all three sources was recorded by weighing the containers before and after the 30-min test, collecting and replacing any food or wooden blocks spilt from the Petri dish during the test session. In addition the animals were video-recorded during the test sessions. The tapes were later scored for the amount of time spent in contact with the substrates presented in both dish and hopper.

2.2.3. Drinking manipulation

The subjects had free access to food and water at all times except when they were in the test cages. The test cages were comprised of a standard cage unit with a stainless steel nozzle attached to one side wall. The nozzle was connected via polythene tubing to a reservoir of solution, propelled by a peristaltic pump controlled by a microprocessor system [3]. Licks were detected by a change in capacitance of the nozzle, and used to control the pump such that the pump would be turned on for 0.5 s if any lick were detected during the preceding 0.5 s. The recording software maintained independent records of pump activations and

licks at the spout to a resolution of 10 ms. Pump activations were used as a measure of intake; the pumps delivered 3.6 mL/min; this rate is just below the maximal rate at which the rats can drink from such a nozzle. Thus, there was almost no spillage, and the duration of the pump activation gives an accurate measure of actual consumption (30 μ L/0.5 S pump activation). On the first training day, the rats were trained to lick for a glucose/saccharin solution (18 g/L glucose, 1.23 g/L saccharin) in a 15-min training session. This was repeated for three daily sessions and then the session duration was increased to 30 min. The subjects had five more daily training sessions of 30 min before the test sessions, which followed either baclofen or saline infusion. Data from two subjects were excluded due to a technical problem with computing hardware.

The data from the drinking test sessions were processed in two ways. First, the durations of pump activation were summed into 1-min bins to give a direct measure of intake. Second, the records of individual licks were parsed into a series of bouts, and the intervals between them by using a time criterion of 250 ms; bout size was then defined as the number of licks within the bout. This criterion was judged most appropriate, as it lay just beyond the point of major inflection in the log-survivorship curve [15,16], however, the analysis was repeated for criteria of 500 and 1000 ms to check whether the results were highly dependent on the chosen criterion.

2.3. Data analysis

The data from the first feeding manipulation were analyzed using one-way analyses of variance (ANOVA) comparing the performance under drug with the vehicle control. In the second feeding manipulation, the data were analyzed untransformed using a two-way repeated-measures ANOVA with the factors group (chow versus wood versus nothing) and treatment (drug versus saline). The drinking data were analyzed untransformed; all analyses were performed using Genstat 5 [17].

2.4. Histology

After the behavioural observations had been completed, the rats were rapidly killed in a gradually rising concentration of CO₂ and transcardially perfused with 10% formol saline. Their brains were removed and stored in formol saline for at least 72 h. They were then blocked and sectioned at 60 μ m on a freezing microtome. All relevant sections were mounted and stained with thionin for verification of cannula placement. Locations of injection sites were taken as the lowest boundary of gliosis below the cannula.

3. Results

3.1. Histology

The targeted injection site was the posterior ventromedial nucleus accumbens shell, below the level of the anterior

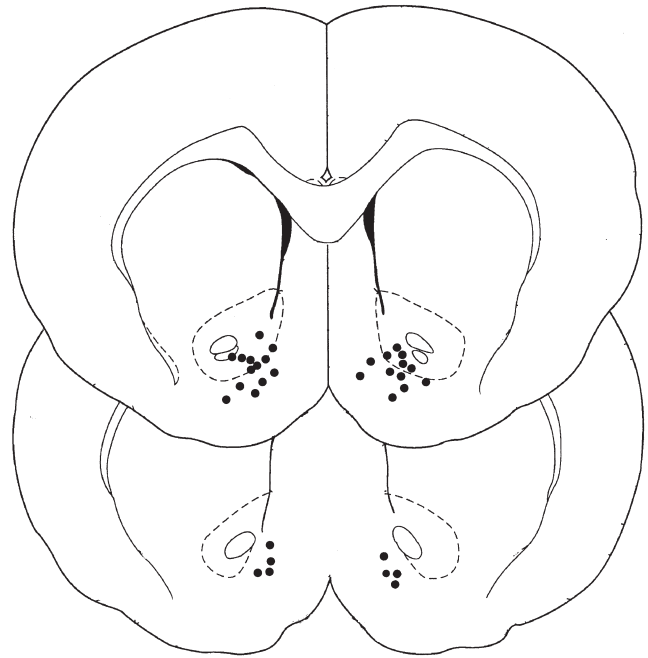


Fig. 1. Injection sites (see text) are plotted on drawings taken from Paxinos and Watson [14]; bregma +0.70 and +1.20 mm.

commissure. All the rats were likely to have had injection sites either within, or within 0.6 mm of, the boundary of the structure (Fig. 1) and, importantly, there was no obvious relationship, at an individual level, between cannula placement and the magnitude of the facilitation of food intake.

3.2. Feeding manipulation 1

The first manipulation with solid food provided a simple comparison of chow consumption from a Petri dish on the base of the cage after baclofen or saline treatment. The mean amount of chow eaten under drug was significantly greater than that eaten under saline infusion [mean and SEM: baclofen 4.7 g \pm 0.6; saline 0.6 g \pm 0.3, $F(1, 16) = 35.75$ $p < 0.001$]. There was no effect of either treatment on the consumption of food from the suspended food hopper ($F < 0.5$, NS) or on drinking from the water bottle ($F < 0.5$, NS), despite the large quantity of dry chow that was consumed from the Petri dish.

3.3. Feeding manipulation 2

In the second experiment, subjects also consumed significantly more of the chow when infused with drug rather than saline, $F(1, 5) = 17.31$, $p < 0.01$. In addition, the subjects showed no enhancement of water drinking under the drug condition, $F(1, 5) = 0.60$, NS), despite consuming large quantities of dry food. This finding is in agreement with Experiment 1. The source of the chow that was consumed in the baclofen-treated groups depended on the contents of the Petri dish (Fig. 2). When the Petri dish contained laboratory chow, this was eaten to the virtual exclusion of

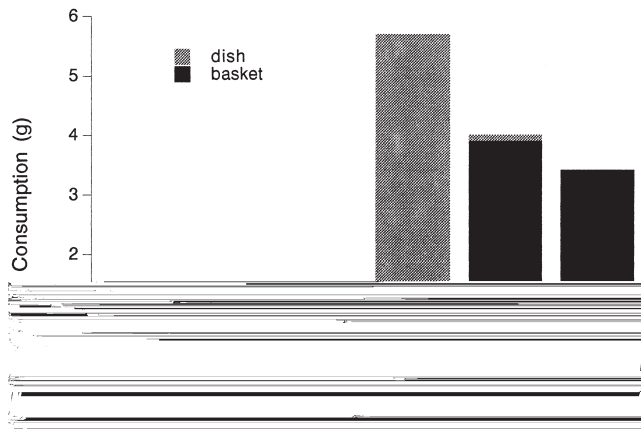


Fig. 2. Effects of bilateral baclofen infusion on food intake in feeding manipulation 2. Condition C: chow was present in both dish and basket; condition W: wood in dish and chow in basket; condition N: nothing in the dish and chow in the basket.

the alternative source, whereas, if the dish contained the wooden blocks or nothing, then the subjects ate from the hanging food hopper [consumption from dish: group \times drug, $F(1, 5) = 27.19$, $p < 0.003$; consumption from basket: group \times drug, $F(2, 10) = 4.19$, $p < 0.05$]. Drug treatment had no effect on water consumption in any condition [group \times drug interactions, $F(2, 10) = 1.57$, NS].

Scoring of the videotapes recorded following baclofen treatment indicated that the intake figures were a good representation of the behavioural response towards the different food/nonfood objects during the 30-min test session. When chow was provided in the dish, the animals spent substantially more time at the location (dish: 557 s; hopper: 41 s; $p < 0.02$ Wilcoxon test). However, when wooden blocks were provided in the dish this preference was reversed (dish: 57 s; hopper: 611 s; $p < 0.02$ Wilcoxon test).

3.4. Drinking manipulation

There was no indication of a difference in response to baclofen that depended on whether the present test preceded or followed testing with solid food, and the following results are for the pooled data set. In contrast to the data from the two feeding manipulations, the total consumption of the palatable liquid was not affected by the baclofen infusion, $F(1, 24) = 0.01$, NS). In addition, when the cumulative intake curves were calculated there was no suggestion of an effect of baclofen infusion (Fig. 3 and Table 1).

An analysis of the licking data indicated that baclofen had no effect on the median interlock interval (Table 1), but that it increased the number of bouts of licking, $F(1, 10) = 7.71$, $p < 0.02$, and decreased the size of those bouts, $F(1, 10) = 7.33$, $p < 0.02$, thus counteracting the change in bout number (Table 1). The reported data use a bout criterion of 250 ms [5,18]; a similar, and a similar significant effect was present when the data were parsed with a 500-ms criterion; the effect became nonsignificant with a criterion of 1000 ms.

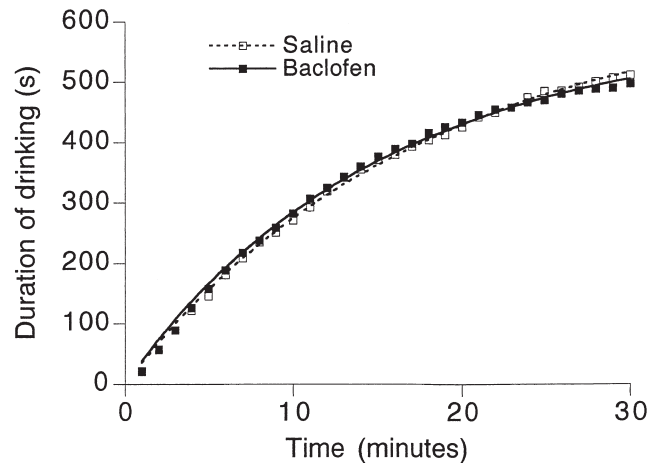


Fig. 3. Cumulative intake curve in the drinking manipulation. The cumulative duration of drinking is shown following treatment with baclofen or saline. The smooth curves are plotted from the best fitting negative exponentials (for parameters, see Table 1). The volume consumed can be estimated from the duration of drinking (see text); 600 s equates to a volume of 35 mL.

4. Discussion

We have confirmed that infusion of the GABA_B agonist baclofen into the posterior nucleus accumbens shell produces a robust stimulation of food intake. In addition, we have shown that feeding responses are not directed at similarly shaped wooden pellets, and that the response is directed at the most immediately accessible appropriate food source; towards food in a dish on the cage floor, if available, but towards food in a suspended hopper if either wooden blocks are presented in the floor dish, or if it is empty. Taken together, these data indicate that the potent increase in food intake produced by infusing the nucleus accumbens with baclofen is unlikely to be explained by direct induction of a motor stereotypy for chewing. In agreement with previ-

Table 1
Drinking paradigm

	Saline	Baclofen	(SED)	Sig
Mean duration of drinking (s)	499	531	(34)	NS
Mean interlick interval (ms)	140	138	(37)	NS
Cumulative curve fit parameters				
Asymptote	631.2	586.1		
Slope	0.0571	0.0663		
Microstructural analysis				
Mean bout size (licks)	19.2	15.2	(1.4)	*
Number of bouts	164	212	(17.2)	*

Data from the drinking paradigm for which tests lasted 30 min: mean duration of drinking is shown in seconds (2.5 g fluid delivered per minute) and mean interlick interval in milliseconds. Cumulative curve-fit parameters are for the best fitting negative exponential (6), and microstructural analyses are for a bout criterion of 250 ms. Saline: 0.5 μ l/side over 30 s; baclofen 94 ng baclofen in 0.5 μ l saline/side over 30 s; SED: standard error of the difference between means; * $p < 0.02$.

ous data [13], we observed no concurrent stimulation of water intake during these tests, despite the consumption of a large quantity of dry chow. It might be argued that our animals should also have been tested with wooden blocks in the absence of food. However, because the animals were well habituated to the presence of food in the test situation, which was identical to the home cage apart from the presence of the Petri dish, its absence would have been very likely to induce a frustration response that included chewing at nonreinforcing objects present in the usual food location [19]. We therefore, rejected a condition of this type as likely to give uninterpretable results.

In contrast, in a separate test in which the rats were allowed to consume a palatable glucose/saccharin solution, baclofen, had no effect on either total intake or on the shape of the cumulative intake curve [20]. This lack of effect was found regardless of the order in which the animals received the drinking manipulation, and, therefore, cannot be ascribed to any increasing ineffectiveness of infusions later in the series. A microstructural analysis of licking indicated that baclofen had a clear effect on bout structure; individual bouts of licking were shorter and increased in number to provide an overall compensation in intake. This finding also suggests that there is no enhancement of palatability estimation by baclofen. Consumption of more palatable (e.g., sweeter) solutions and benzodiazepine treatment are both associated with increases in bout size [4,18].

4.1. Pharmacological considerations

Comparison of the effect of baclofen on food intake with other drug-induced effects on consumption provides some interesting contrasts. Although the effect on the intake of solid food is as robust as that observed with benzodiazepines [4,18], there is no similar effect on the ingestion of a palatable fluid. Because the increase of fluid intake induced by benzodiazepines was found in nondeprived animals [4], as here, and we used the same palatable glucose/saccharin solution in the present experiment, it is unlikely that our failure to find an increase in fluid intake is due to a ceiling effect in our animals.

Converging evidence from microstructural analyses, taste reactivity studies, and intracerebral administration suggest that the benzodiazepine effect is mediated by effects on taste processing within the brain stem that lead, at the behavioural level, to enhanced estimates of palatability [18], which may be expected to produce increases in the consumption of both solid and liquid food. The contrast between the generalisation to palatable fluids seen with benzodiazepine infusion and its absence with baclofen infusion makes a simple explanation in terms of changed palatability estimation an unlikely candidate hypothesis for the effects of baclofen on food intake described here and elsewhere [13]. The contrast with effects of opioid receptor stimulation is also striking. Again, it is argued that these effects depend on changes in palatability estimation [8], even when the agonist drug is administered directly into the nucleus ac-

cumbens [7]. On both behavioural and neurochemical grounds, the baclofen effect seems closer to the stimulation of food intake produced by systemic or intraraphe administration of 8-OH-DPAT. This effect is also robust for ingestion of solid food, but harder to demonstrate for fluids [2,9], and several lines of evidence suggest that the effect depends, in part, on modulation of neurochemical systems within the nucleus accumbens [21,22].

It seems likely that the present effect is mediated by the same behavioural and neurochemical mechanisms as are involved in the increase in food intake produced by AMPA antagonists injected into the same compartment of the accumbens [23]; dry food consumption was substantially increased with no effect on water intake. Intake of palatable, but dilute, sucrose solution was unaffected, although the usual enhancement of intake over water was clearly evident [24].

4.2. Neural considerations

At a neural level, it is known that there is a substantial, though diffuse, projection from the nucleus accumbens to the lateral hypothalamus [25]. Stratford and Kelley [13] argue that, in satiated animals, glutamatergic afferents to the nucleus accumbens produce activation of this GABAergic projection to the lateral hypothalamus, and reduce ingestive responses; thus, muscimol infusions into the lateral hypothalamus inhibit feeding, although the same agonist stimulates feeding when infused into the medial hypothalamus [26]. Baclofen may activate presynaptic GABA receptors on the glutamatergic afferents that would presumably normally be activated by axon collaterals of the spiny projection neurons [27], and hence, reduce activation of the projection neurons leading to a disinhibition of feeding at the level of the lateral hypothalamus. It may seem puzzling that activation of such a general mechanism can lead to an apparently selective effect on feeding. For example, we saw no activation of locomotion, which might be expected given that there is a similar GABAergic projection from nucleus accumbens to ventral pallidum that is known to modulate locomotor activity [27], but this might be explained by differential shell/core connectivity. It is also interesting that Shoab et al. [28] report that intraaccumbens infusions of baclofen at similar doses to those used here reduce cocaine self-administration. Systemic baclofen administration also reduces cocaine self-administration, but has little effect on food-maintained responding [29]. These findings are consistent with the suggestion that enhancement of GABAergic function by the GABA-transaminase inhibitor vigabatrin may both reduce cocaine-reinforced place preference and depress the effects of cocaine on nucleus accumbens dopamine function; however, similar doses of vigabatrin had no effect on a food-reinforced place preference [30]. Given the frequent parallels between actions of drug and natural reinforcers, such as food, at this neural level, behavioral effects in opposing directions are unexpected, and well worth further investigation.

In summary, stimulation of GABA_B receptors in the shell region of the nucleus accumbens produces a robust feeding response [13]. We have demonstrated that this effect is behaviorally specific, and is unlikely to be accounted for by facilitation of the motor patterns, such as gnawing and chewing, that are associated with food consumption. The response is likely to be associated with both an increased likelihood of initiation of a meal and also an insensitivity to some of the interoceptive cues that would usually serve to terminate feeding. The relevance of these effects to the endogenous control of meal initiation and termination will need to be established using different experimental approaches, but our data support hypotheses suggesting that the nucleus accumbens plays an important role in the neural systems that control ingestive behavior in the rat.

Acknowledgments

Our thanks to Ian Roughsedge for support and Lynda Penfold for rearing and caring for the animals.

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