The control of ingestive behavior by the median raphe nucleus

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For a period of 20 years, from 1974 to 1994, I had the great pleasure of interacting with Jack Davis on an almost daily basis, first as a graduate student and later as a faculty member. Jack’s work has, of course, had a tremendous influence on the field of ingestive behavior and it should, perhaps, not be too difficult to envision how great his influence must have been on someone who occupied the office next to his for a period of many years. During much of this time my research centered on studies of the behavioral effects produced by various experimental manipulations of the median raphe nucleus (MR), a structure located in the paramedian mid-brain tegmentum which is one of the major sources of serotonergic projections to the forebrain. I should like here to review some of the results obtained in my laboratory relating to role of this nucleus in the control of feeding and drinking.

MR lesions and ingestive behavior

Hints that the MR may play a role in the control of ingestion arose initially from studies on the effects of nonspecific lesions. Electrolytic or radiofrequency lesions involving the MR had been reported, for example, to produce transient hyperdipsia and hypophagia, to alter the “circadian” distribution of food intake, to exaggerate prandial water intake, to reduce body weight, and to prevent the development of obesity following medial hypothalamic lesions (Asin, 1980; Asin & Wirtshafter, 1982; Coscina, 1981; Coscina et al., 1972; Kostowski et al., 1968; Lorens et al., 1971). These findings must be interpreted cautiously, however, since the region of the MR is traversed by a number of fiber systems whose destruction might play a role in some of these effects. This point is illustrated by Fig. 1 which shows some data collected with Karen Asin, another protegée of Jack, comparing the effects of electrolytic and excitotoxic lesions of the MR on body weight. It can be seen that electrolytic MR lesions produced a modest, but persistent, reduction of body weight relative to control animals, a pattern we have observed many times and which is suggestive of a reduction in the body weight “settling point” (Davis & Wirtshafter, 1978; Wirtshafter & Davis, 1977). In contrast, fiber sparing lesions of the MR produced by local injections of ibotenic acid had only a small effect on body weight which disappeared by the end of the testing period. Although their effects on body weight differed, the electrolytic and ibotenate lesions produced equivalent reductions in forebrain serotonin levels, suggesting that they damaged output neurons of the MR to a similar degree (Asin & Fibiger, 1983). These findings indicate that the effects of the electrolytic lesions on body weight are probably largely due to damage to fibers of passage, a likely possibility being components of the ascending trigeminal system which decussate through the ventral portion of the rostral MR.

Acute inhibition of MR cells induces feeding and drinking

Most of our studies on the role of the MR in ingestive behavior have employed the technique of intracranial drug injections, a method which minimizes the possibility of effects due to an involvement of fibers of passage. In our first studies...
on this topic we were able to demonstrate that intra-MR injections of the GABA_A agonist muscimol lead to very large increases in both food and water intake (Klitenick & Wirtshafter, 1988). These effects were anatomically localized to the MR since much smaller responses were seen following infusions into adjacent structures including the dorsal raphe nucleus and the ventral tegmental area (Klitenick & Wirtshafter, 1988). Since GABA receptors are almost always inhibitory, it seemed likely that these effects resulted from a suppression of MR output neurons. These results suggest that the MR normally exerts an inhibitory control over ingestive behavior, a conclusion which is further supported by the finding that intra-MR injections of several excitatory amino acid (EAA) agonists are able to suppress deprivation induced food and water intake (Wirtshafter & Krebs, 1990). Conversely, intra-MR injections of several different EAA antagonists are able to stimulate feeding and drinking (Wirtshafter & Krebs, 1990; Wirtshafter & Trifunovic, 1988), presumably by “disfacilitating” MR cells by blocking tonic excitatory inputs.

**Behavioral characterization of the effects of MR inactivation**

Rats tend to drink when consuming solid foods; as a result any treatment which increases food intake will also be likely to increase fluid intake. It is possible, therefore, that intra-MR injections of muscimol affect drinking only indirectly, as a consequence of their effect on food intake. In order to rule out this possibility we examined the effects of muscimol injections on water consumption in the absence of food (Klitenick & Wirtshafter, 1989). These experiments indicated that inhibition of MR cells increases drinking to the same extent whether or not food is present, and thus demonstrate that the MR has a direct influence on water consumption. This conclusion is further supported by studies in which we used osmotic minipumps to continuously infuse muscimol into the MR at a rate of 6.25 ng/h (Stratford & Wirtshafter, 1990). Under these conditions muscimol induced huge increases in water intake, daily consumption frequently exceeding the animals’ body weights, whereas much smaller effects were produced on food intake. It is possible that these quantitative differences observed following chronic infusions may be related to reports that electrolytic MR lesions induce hyperdipsia, but not hyperphagia (Asin, 1980; Lorens et al., 1971; Coscina et al., 1972).

In addition to increasing oral behaviors, muscimol injections also induce very robust increases in locomotor activity (Sainati & Lorens, 1982; Wirtshafter & Klitenick, 1990; Wirtshafter et al., 1987). One could speculate, as was once popular with regards to the lateral hypothalamus, that inactivation of the MR may result in a state of “non-specific arousal” which might “funnel” into any behavior supported.
by the environment. The effects of intra-MR injections on activity and ingestive behavior can, however, be at least partially dissociated. Intra-MR injections of the delta-opiate agonist DPDPE and the substance P agonist senkitide both produce marked hyperactivity, but the former drug has no effect on feeding and drinking, while the latter actually suppresses ingestion (Kliténick & Wirtshafter, 1995; Paris et al., 1991). While these findings do not prove that the hyperactivity and ingestion induced by muscimol are unrelated, they certainly indicate that increases in food and water intake are not automatic consequences of raphe mediated hyperactivity.

The behavioral energization produced by intra-MR injections of muscimol is not restricted to increases in feeding, drinking and locomotion; in the absence of both food and water, these injections will induce gnawing at wood blocks (Kliténick & Wirtshafter, 1989) and non-consumptive shredding of paper (unpublished observations). These results might be taken to suggest that intra-raphe muscimol injections induce a generalized potentiation of oral behaviors, rather than a specific increase in food intake. It is interesting, however, that gnawing can also be induced by several other central manipulations which induce feeding, including electrical stimulation of the lateral hypothalamus and injections of norepinephrine into the paraventricular nucleus of the hypothalamus (Swiergiel & Peters, 1987). In contrast, several other treatments, including injections of cyclic-AMP into the perifornical region and of excitatory amino acid agonists or antagonists into the perifornical hypothalamus or the nucleus accumbens shell, respectively, are able to induce feeding in the absence of gnawing (Gillard et al., 1998; Stanley et al., 1993; Stratford et al., 1998). At the present time it is difficult to speculate as to the relation between feeding and non-consumptive gnawing behavior; this task would be greatly facilitated were more information available about the stimuli which control gnawing in normal animals. It is possible, for example, that manipulations like food deprivation might act to enhance both feeding and gnawing of inedible objects.

It should be stressed that the ability of intra-MR injections to increase food intake is certainly not a simple consequence of the induction of chewing behavior since these injections also increase the intake of liquid diets (Stratford et al., 1991). In fact, in studies conducted with Tom Stratford and Jack Davis, we were able to show that muscimol induces a larger increase in the intake of a 10% sucrose solution than does in the intake of a 1.7% solution (Stratford et al., 1991), a result which demonstrates that the subjects were not simply treating the palatability of the solutions, because, as Davis and Levine (1977) showed in a classic paper, altering the palatability of an ingested fluid does not typically alter the proportional rate at which licking decays.

Although the pace of decay may be slowed, it is apparent that rate of intake is maximal in the period shortly after intra-MR drug injections and progressively decreases thereafter. This slowing could indicate the development of “satiation”. Alternatively, it is possible that it may simply reflect a wearing off of the drug’s effect with time. In order to investigate this issue, Stratford, Davis and I further examined the time course of licking in rats ingesting a 10% sucrose solution. Rats were tested for a 1-h period beginning either immediately after injections of saline or of muscimol or 30 min following injections of muscimol, the delay period being spent in the animals’ home cages with food and water unavailable. As can be seen in Fig. 2, delaying testing had virtually no effect on the rate of decay of licking, demonstrating that this decay is a function of the time spent drinking, not of the time since injection. This pattern of results suggests that muscimol induced feeding is sensitive to some of the post ingestive stimuli which control other types of feeding behavior. This conclusion is further supported by studies in which we have demonstrated that a number of different anorectic drugs are able to suppress muscimol induced feeding at doses similar to those at which they suppress deprivation induced ingestion (unpublished observations). In the case of phenylpropanolamine these effects were strikingly specific; this drug produced a dose dependent suppression of muscimol induced feeding while having no effect on water intake. (This finding provides further evidence that the effects of raphe inactivation on drinking are not secondary to effects on feeding.) It is interesting that phenylpropanolamine has previously been shown to induce a similarly selective suppression of feeding, but not drinking, elicited by lateral hypothalamic stimulation (Hoebel et al., 1975). In contrast, a number of other anorectic drugs, including fenfluramine, amphetamine, haloperidol, and the CCKA agonist A-71623, all act to suppress muscimol induced drinking as well as feeding.

Deprivation of food or water, of course, not only induces ingestive behavior, but also energizes behaviors reinforced by the presentation of a suitable ingesate; in other words, deprivation conditions are able to imbue environmental stimuli with reinforcing or rewarding properties. In order to determine whether inactivation of the MR can have similar consequences we examined the effects of intra-MR injections on operant behavior (Wirtshafter et al., 1989). Food deprived rats were trained to respond for food reward in a standard operant box equipped with two levers; depressing one of the levers delivered food whereas depressing the other had no effect. After a stable baseline of responding had been achieved, animals were taken off food deprivation for 1 week during which time both standard lab chow and the Bio-serve pellets used in operant training were available. At the end of this period, rats were given intra-MR injections and replaced in the operant boxes. Relative to saline infusions, injections of muscimol resulted in a large increase in responding on the reinforced lever, while having little effect on the non-reinforced lever. Furthermore, discontinuation of reinforcer delivery resulted in a rapid extinction of the operant behavior, demonstrating that the occurrence of lever pressing under these conditions was indeed dependent on its consequences. These findings demonstrate that inactivation of
the MR not only induces ingestive behavior per se, but can also motivate arbitrary behaviors reinforced by food delivery.

To summarize the results presented so far, pharmacological inactivation of the MR leads to remarkable increases in feeding and drinking and the magnitude of these effects can be altered by a number of variables, such as the palatability of the ingestate, the amount previously consumed, and the presence of anorectic drugs, which also control ingestion induced by other means. In addition, inactivation of the MR, like food deprivation, is able to motivate food reinforced operant behaviors. This pattern of effects suggests that inactivation of the MR may induce ingestive behaviors through pathways involved in other types of feeding and drinking. Characterization of the precise nature of the effects produced by intra-MR injections can obviously play an important role in attempts to understand the syndrome, but it would be rather naive to expect that the behavioral effects produced by any central manipulation would necessarily exactly mimic those produced by peripheral manipulations, such as food deprivation. It is likely that central alterations can modify behavior in ways which peripheral ones cannot, and this is one of several reasons why it is not likely to be constructive to attempt to map the effect of every central manipulation onto behaviorally, or introspectively, derived concepts such as “thirst” or “hunger”. In some cases, however, detailed behavioral studies may allow certain correspondences to be rejected. For example, the behavioral data described above suggest that muscimol injections do not simply make food “taste better”.

Role of serotonin in mediating the effects of MR inactivation

The MR is best known as one of the major sources of ascending serotonergic projections to the forebrain, and, as a consequence, many workers have assumed that any effect produced by manipulations of the MR must result from alterations in serotonergic transmission. In fact, however, a substantial majority of MR cells utilize transmitters other than serotonin (Leger & Wiklund, 1981) and these non-serotonergic neurons may mediate many effects obtained from the MR. The best studied example of this involves locomotor activity: although lesions of the MR, or intra-MR injections of inhibitory compounds, induce dramatic hyperactivity, a large body of evidence indicates that effect is not due to destruction or inhibition of serotonergic neurons (Asin & Fibiger, 1983; Geyer et al., 1980; Klitenick & Wirtshafter, 1995; Lorens, 1978; Paris & Lorens, 1987; Shim et al., 1997; Wirtshafter et al., 1987, 1993). Given this background, it may be worthwhile to examine the available evidence bearing on the question of serotonergic involvement in the hyperphagic and hyperdipsic effects of intra-MR injections.

The strongest reason, other than general plausibility, for believing that inhibition of serotonergic neurons may underly the effects of muscimol is that hyperphagia can also be produced by intra-MR injections of the 5-HTA agonist 8-OH-DPAT (Bendotti & Samanin, 1986; Currie & Coscina, 1993; Fletcher, 1991). The 5-HTA receptor functions as an
inhibitory somatodendritic autoreceptor and dialysis studies have directly shown that intra-MR injections of 8-OH-DPAT suppress forebrain serotonin release to a similar extent as do muscimol injections (Bonvento et al., 1992; Shim et al., 1997). It should be noted, however, that 5-HT1A receptors are also found postsynaptically on non-serotonergic neurons in the MR (Sotelo et al., 1990) and it is possible that an action on these receptors may be involved in the effects on feeding. More importantly, examination of published data suggests that the magnitude of the hyperphagia produced by 8-OH-DPAT is much less than that seen after muscimol, a quantitative difference we have confirmed by direct comparisons (unpublished observations.) Muscimol and 8-OH-DPAT induced feeding are also differentially affected by the time of testing. We have found that muscimol injections induce equivalent increases in food intake during the day and during the period shortly after light offset (Klitenick & Wirtshafter, 1987). In contrast, Currie and Cosicina (1993) have reported that intra-MR 8-OH-DPAT injections actually decrease food intake in the early portion of the dark period. Finally, whereas the effects of muscimol on drinking are at least as pronounced as its effects on feeding, intra-MR 8-OH-DPAT does not appear to stimulate water intake (Tomkins et al., 1994). These results indicate that the effects of muscimol and 8-OH-DPAT on ingestive behavior are not identical and that the actions of muscimol are likely to be mediated at least partially through cell populations not affected by 8-OH-DPAT. Several other lines of evidence support this conclusion. For example, Mark Klitenick and I found that intra-MR injections of muscimol produce equivalent increases in food and water intake in normal rats and in subjects previously depleted of serotonin by means of intra-raphe injections of the neurotoxin 5,7-dihydroxytryptamine (Klitenick & Wirtshafter, 1987). Again, vigorous feeding and drinking can be induced by intra-MR injections of the GABA_B agonist baclofen (Wirtshafter et al., 1993), even though intra-MR injections of baclofen do not alter forebrain serotonin release (Shim et al., 1997; Wirtshafter et al., 1993) and some data suggest that GABA_B receptors may not be located on serotonergic neurons in the MR (Mennini et al., 1986).

The available data then support the view that nonserotonergic cells are importantly involved in the mediating the influence of the MR on the intake of food and, especially, water. This is not to deny a role for serotonergic neurons, only to stress that by equating the MR with its serotonergic cells one runs the risk of drastically underestimating the behavioral importance of this nucleus. Since the majority of cells in the MR are non-serotonergic, it is unlikely that the functions of this structure could be completely elucidated by studies which concentrate exclusively on its serotonergic elements, as do the majority of those reported in the literature. Conversely, it is likely that understanding of the function of serotonergic MR neurons would be advanced by recognizing that they are but one of several populations of cells found in this region.

**How does inactivation of the MR stimulate ingestive behavior?**

A number of studies have demonstrated that the release of dopamine in the nucleus accumbens can be increased by several feeding inducing treatments including intra-hypothalamic injections of norepinephrine, galanin and sulpride, and electrical stimulation of the lateral hypothalamus (Hanjal et al., 1997; Parada et al., 1995; Rada et al., 1998). These findings suggest that the feeding induced by these manipulations may be mediated through accumbens dopamine release, a possibility supported by the fact that injections of dopamine agonists directly into the accumbens are able to stimulate food intake (Swanson et al., 1997). In this context, it is striking that accumbens dopamine metabolism is also increased following intra-MR injections of a number of compounds which stimulate ingestive behavior including muscimol, the GABA_B agonist baclofen and the EAA antagonist 2-amino,5-phosphonovaleric acid (Wirtshafter & Trifunovic, 1992; Wirtshafter et al., 1989, 1993), but not 8-OH-DPAT (Hillegaart et al., 1990). (It should be noted that nothing is known about the pathways or mechanisms through which inactivation of the MR alters dopamine turnover.) On the other hand, we have found that intra-MR injections of the delta opiate agonist DPDPE produce a robust increase in accumbens dopamine turnover, but have little effect on food or water intake (Klitenick & Wirtshafter, 1995). This finding suggests that alterations in accumbens dopamine release cannot entirely account for the feeding elicited from the MR, although it is certainly possible that they might play some role. It is less likely that increases in accumbens dopamine could be critically involved in elicited drinking since the effects of intra-accumbens administration of dopaminergic and other drugs appear to be relatively specific for feeding (Stratford & Kelly, 1997; Swanson et al., 1997). In addition, injections of galanin into the paraventricular nucleus, which increase accumbens dopamine release, stimulate feeding but not drinking (Kyrkouli et al., 1990), further suggesting that stimulation of accumbens dopamine receptors is not a sufficient stimulus for the induction of drinking.

Anatomical studies have shown that the MR is heavily interconnected with a number of forebrain structures which are believed to play an important role in the control of food and water intake. For example, the MR both projects to, and receives projections from, the lateral hypothalamus, the perifornical region, the preoptic area and the subfornical organ (Aghajanian & Wang, 1977; Berk & Finkelstein, 1982; Lind, 1986; Vertes et al., 1999). Since it is well known that feeding or drinking can be induced by electrical or chemical stimulation of cells within these regions, it is possible that the effects of MR inactivation might be mediated through a disinhibition of cells in some of these areas. This conclusion is supported by studies conducted with Tom Stratford which demonstrated that electrolytic lesions of the subfornical organ and excitotoxic lesions of the lateral hypothalamus both drastically attenuate the induction of drinking by intra-MR injections of muscimol (Stratford & Wirtshafter, 1992). My student, David Cook, and I are currently conducting similar studies with regard to feeding behavior. One could speculate that the MR may send inhibitory projections to several different populations of hypothalamic and forebrain neurons involved in feeding, in drinking, and perhaps in other motivational systems such as those underlying sexual behavior and
locomotor activity. Inactivation of the MR might then result in the release of a number of behaviors mediated through these various sets of forebrain neurons. Basal forebrain and hypothalamic structures in turn project to the region of the MR, and electrical stimulation of the lateral hypothalamus has been shown to increase glucose utilization in the MR (Roberts, 1980). If activation of hypothalamic and basal forebrain motivational mechanisms were to result in an excitation of MR cells mediated through these descending pathways, the hypothalamus-raphe-hypothalamus circuit might then act as a negative feedback loop which would tend to restrain or, perhaps, focus motivational activation. Obviously, the available data fall far short of proving this hypothesis, but it may serve as a useful working model for the functioning of hypothalamic-MR circuitry which can account for the robust and pervasive influence exerted by the MR on a variety of behaviors.


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