dOG-P components reveals that both the rate of uptake and final steady-state concentration of free 2-dOG are essentially the same in all four cell types. The increased total intracellular 2-dOG in SV-3T3 and 3T6 is accounted for entirely by increased amounts of the phosphorylated sugar (2-dOG-P) in these density-independent cell types.

The final steady-state concentration of free 2-dOG in all cases was approximately 11 nmole per milligram of cell protein. If one assumes that protein accounts for 60 percent of the total dry weight of the cells, that the cell is 80 percent water, and that all the cell water is available to external solute, this would represent an intracellular concentration of 1.7 m*M* 2-dOG, a value very close to the external concentration.

Since mammalian cells other than kidney and intestinal epithelial cells transport sugars by a facilitated diffusion process that yields a final equilibrium distribution of substrate and does not involve concentrative uptake against a gradient (*16*), we take the rate of appearance of the unaltered free 2-dOG molecule in the intracellular pool to be a measure of the transport process. Thus we suggest that the increased total uptake of 2-dOG measured in SV-3T3 and 3T6 cells is not a result of enhanced transport of the sugar, but a consequence of increased phosphorylation by intracellular kinases subsequent to transport. This effect is not specifically a function of SV40 virus transformation, since it is absent in the flat revertant (SV-3T3-FL) that retains the viral genome, and it is present in 3T6 cells that contain no DNA tumor virus. We postulate that the initial phosphorylation of sugar may be one of the series of metabolic reactions that is modulated in accord with growth rate, which has been referred to as the "pleiotypic response" (*17*) and which may become perturbed in a number of ways, including virus transformation.

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14. Cells were grown in Dulbecco's modified Eagle's medium supplemented with 5 percent (by volume) of calf serum on glass cover slips 15 mm square, as described by D. O. Foster and A. B. Pardee [*J. Biol. Chem.* **244**, 2675 (1969)]. Isotope solutions were made up in glucose-free Hanks solution. Protein in cells grown on cover slips in the same dish as cells used in each experiment was determined by the method of O. H. Lowry, N. J. Rosebrough, A. L. Farr, and R. J. Randall [*J. Biol. Chem.* **193**, 265 (1951)].
15. Apparent K_i was calculated from the formula

$$K_i = \frac{I}{\frac{K_p}{K_m} - 1}$$

where I is the concentration of inhibitor, and K_p and K_m are values read graphically as the intersection of the lines with the abscissa in the presence and absence of inhibitor, respectively.
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20. We thank Dr. R. Pollack for cultures of SV-3T3 and SV-3T3-FL, Dr. H. Green for cultures of 3T3 and 3T6 cells, and M. McCloud and M. A. Brustalon for technical assistance. Supported by NSF grant GB 31543, Damon Runyon Memorial grant DRG-1191, NIH grant AI-10096, and the University of Connecticut Research Foundation. C.C. is the recipient of a research career development award from the National Institute of Allergy and Infectious Diseases.

27 October 1972

Putamen: Activity of Single Units during Slow and Rapid Arm Movements

Abstract. *The activity of putamen neurons was studied in a monkey during the performance of both slow and rapid arm movements. More than half of all movement-related units discharged preferentially in relation to slow movements and less than 10 percent in relation to rapid movements. These findings indicate that at least a portion of the basal ganglia (the putamen) is primarily involved in the control of slow movements and are consistent with the hypothesis of Kornhuber that the primary motor function of the basal ganglia is to generate slow ("ramp") rather than rapid ("ballistic") movements.*

Clinicopathologic studies in man indicate that the basal ganglia play an important role in the control of movement and posture (*1*). Kornhuber (*2*) has recently interpreted clinical and experimental evidence to indicate that the primary motor function of the basal ganglia is to generate slow ("ramp") movements, whereas the function of the cerebellum is to preprogram and initiate rapid ("ballistic") movements. If this view is correct, one might predict that the activity of basal ganglia neurons would be preferentially related to slow rather than rapid movements. To test this hypothesis, the activity of neurons in the putamen (a prominent portion of the basal ganglia) was recorded in a monkey during the performance of a motor task involving both slow and rapid arm movements.

For these studies a monkey (*Macaca mulatta*) was trained to reach out and grasp a lever and to execute slow and rapid (pushing and pulling) arm movements between two zones 1 cm wide and 5 cm apart. To begin the task, the animal had to move the lever into the starting zone and hold there for an unpredictable period of 2 to 6 seconds. A white lamp indicated to the monkey that the lever was within the correct zone. Then, when a green lamp came on, the animal had to make a slow (ramp) movement into the opposite zone. The movement time between the zones had to be greater than 0.7 second but less than 1.0 second. After executing a slow movement, the animal held again for 2 to 6 seconds within the opposite zone. Now, when a red lamp came on, the monkey had to move the lever as rapidly as possible (ballistic movement) back to the original starting zone.

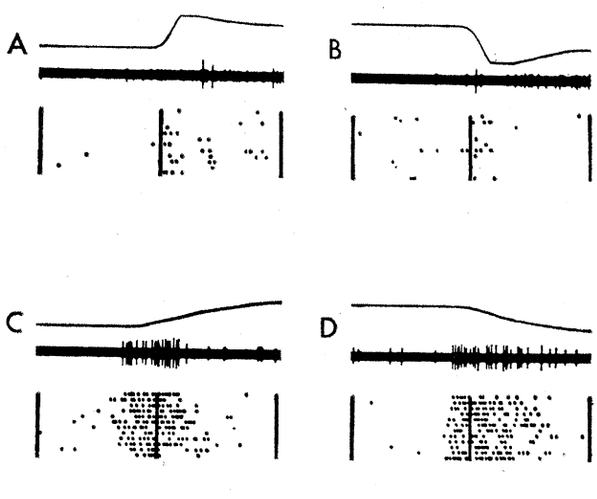
The ballistic movements were arrested by impact against mechanical stops 1 cm beyond each zone. A juice reward was delivered after each rapid movement if the movement time between the zones was less than 140 msec. After the rapid movement, the animal again positioned the lever within the starting zone and the sequence of slow and rapid movements was repeated. By changing the starting zone, it was possible to have the animal make both slow and rapid movements in each direction,

that is, pushing and pulling. A potentiometer was coupled to the axis of the lever in order to monitor the position of the arm during the task. Single unit activity was recorded from the contralateral putamen by using techniques previously described (*3, 4*). Since units in the putamen normally discharge at very low rates during rest, the animal was allowed to perform the task while advancing the electrode in search of movement-related units. Each unit encountered was studied during both slow and rapid movements in each direction.

Ninety-five units in the putamen were found to consistently change their discharge in relation to one or more of the movements. Of these, approximately 50 percent discharged either solely or preferentially in relation to the slow movements, while only 10 percent discharged preferentially during the rapid movements. The remaining units (approximately 40 percent) were active during both slow and rapid movements. An example of the activity of a ramp-related unit is shown in Fig. 1. This unit discharged in relation to slow movements in both directions (Fig. 1, C and D), but was virtually silent during the two rapid movements (Fig. 1, A and B). The onset of unit discharge preceded any change in the position of the arm for ramp movements in both directions. Many ramp-related units discharged for only one direction of movement, as illustrated by the unit in Fig. 2. This unit discharged intensely during the pulling ramps (Fig. 2D) but not at all during the pushing ramps (Fig. 2C). Only one or more spikes occurred in relation to the pulling ballistic movements (Fig. 2B). A weak discharge during the ballistic movement, as occurred in the unit in Fig. 2, was frequently observed in ramp-related units. The unit in Fig. 2 also discharged prior to any movement of the arm.

The present study has revealed rather specific requirements for activation of putamen neurons during movement and has shown the importance of studying the activity of basal ganglia cells during different kinds of movement. Thus, in previous studies (*4, 5*), in which animals were trained only to make rapid movements, a much smaller number of movement-related units was found in the putamen than in the present study. The present findings were striking, therefore, not only in that unit activity was preferentially related to ramp movements, but also in that (unlike previous experiments) so many putamen units became active in relation to the task.

The finding that the majority of movement-related units in the putamen are preferentially active in relation to slow rather than rapid movements lends some support to the suggestion of Kornhuber that the basal ganglia function primarily in the generation of slow movements. However, since previous studies (*4, 5*) indicate that neurons in the pallidum, which gives rise to the bulk of efferents from the basal ganglia, are involved in the initiation of rapid arm movements, and since numerous putamen units in the present study discharged in relation to rapid as well as slow movements, it is clear that the basal ganglia do not function solely in the control of slow movements. The present study suggests, nonetheless, that at least a large portion of the basal ganglia (the putamen) is preferentially involved in the control of slow movements. The view that the basal ganglia function primarily in the generation (that is, initiation) of ramp movements implies not only that the activity of basal ganglia units should be preferentially related to slow movements, but also that the earliest changes in activity of such neurons should precede the onset of movement, that is, the earliest changes in the muscle activity. This second point is not fully settled by the present study since, although many ramp-related units showed changes in activity prior to any change in the position of the arm, precise determinations of the earliest change in muscle activity associated with the ramp movements have not yet been made. Since it has been shown previously that striatal neurons can be activated by stimulation of skin and muscle afferents (*6*), it remains a possibility that sensory feedback might be responsible for these findings. Against this, however, is the fact that it was not possible (in the units tested) to drive ramp-related neurons by passive movement of the limb



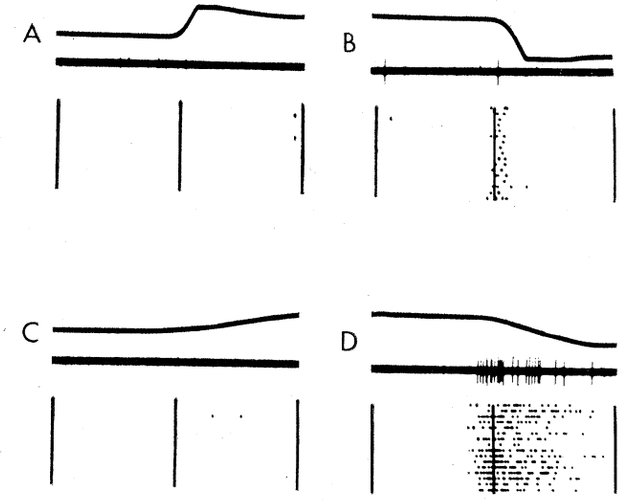


Fig. 1 (left). Activity of a ramp-related unit from the putamen during pushing and pulling ballistic (A and B) and ramp (C and D) movements. For (A) to (D) the upper trace represents the position of the lever during a single trial; the middle trace, the unit discharge for the same trial; and the lower portion, the activity of the unit during 12 successive trials shown in raster form. Each trial is aligned on the time of leaving the zone (center bar). The interval from the center to the margin of the raster is 1 second. The unit discharged in relation to the ramp movements (C and D) but not the ballistic movements (A and B). Fig. 2 (right). Activity of a ramp-related putamen unit during performance of the task. The conventions are the same as for Fig. 1. This unit discharged in relation to the pulling ramp (D) but not to the pushing ramp (C) movements. The unit also discharged weakly during the pulling ballistic movements (B).

or other sensory stimulation. Moreover, the units with clearly demonstrable responses to kinesthetic inputs observed in these studies showed changes in activity during both ramp and ballistic movements.

These findings on the preferential relation of neural activity in the putamen to slow movements may have relevance to the pathophysiology of movement disorders involving the basal ganglia in man. Considerable evidence points to a selective disturbance in slow movements in many of these disorders. Generally speaking, the involuntary movements associated with basal ganglia dysfunction (for example, chorea, athetosis, dystonia) are "slow" in character. Also, in the akinetic syndrome of Parkinsonism the major difficulty appears to be in the initiation of slow movements, such as rising from a chair or bed, turning, walking, and so forth. The initiation of simple rapid movements in Parkinsonism patients appears to be less impaired than one would predict (*7*). Kornhuber (*2*) has suggested that akinesia might result from loss of the ramp-generating mechanisms of the basal ganglia, whereas rigidity, chorea, athetosis, and dystonia might result from various forms of "release" of these same neural mechanisms. The present experiment, indicating that the activity of a large portion of the striatum is preferentially involved in the control of slow movements, is consistent with this view as well as the evidence for involvement of the striatum in the pathogenesis of akinesia as well as rigidity, chorea, athetosis, and dystonia (*1*).

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20 November 1972

Preference Enhancement for Alcohol by Passive Exposure

Abstract. *A large and lasting enhancement of alcohol consumption over control levels is reported after direct infusion of 10 percent alcohol into the stomach of rats for 6 days.*

While it has seemed probable that addiction to alcohol is at least in part due to the development of physiological tolerance to the drug, there have to date been no clear demonstrations that alterations in the blood level of alcohol alone (without concomitant experiential factors of taste and ingestion) were sufficient to produce a lasting enhancement of alcohol preference subsequent to treatment (*1*). Here we report a method capable of producing a lasting enhancement of alcohol preference without concomitant oral stimulation. Not only has the method succeeded in separating out the experiential from the more purely physiological factors in alcohol preference in rats, but it also provides a very fast and convenient way of producing an animal preparation of use in the study of alcohol addiction.

This enhancement of preference has been achieved by prolonged passive infusion of alcohol into the stomach of rats. After recovery from surgical preparation (*2*), the rats were placed in a Bowman restrainer cage (*3*) to adapt for 24 hours. After this initial period each rat was connected to a pump (*4*). Seven rats (Sprague-Dawley, 6 months old) were infused with an alcohol solution (10 percent by volume) at the mean rate of about 45 ml per 24 hours. This infusion continued for 6 days.

All rats were released for 30 minutes per day to enable them to groom themselves and to exercise. Rats were also released if they lost consciousness. They were then allowed to recover outside the apparatus. The rate of infusion was 2.17 ml/hour. Seven control animals were treated similarly except that water was infused instead of the alcohol solution. As these rats never lost consciousness, the amount of water infused averaged about 51 ml. Because of the sedating effect of the alcohol, we believe the stress of the restraint was actually less in the rats infused with alcohol. In contrast with the water-infused controls, it was difficult to elicit a startle reflex in them. Alcohol was never presented to the rats before or during the period of the infusion. At the end of 6 days the infusion was stopped; the animals were then kept in the restraining cage for another 3 days, where they were presented continuously with two nozzles, one providing water and the other a solution of 10 percent alcohol by volume. After 3 days, the rats were placed in ordinary Plexiglas enclosures, still with a continuous choice between the alcohol solution and water. They were maintained in this condition for 14 days. The position of the alcohol tube was randomly changed each day. The rats were given unlimited food throughout the experiment, even during the period of infusion, so that it is difficult to ascribe increases in alcohol consumption to a simple enhancement of caloric need.

The food was Simonsen's White Diet, and enriched nutriment used in breeding. Further, while both alcohol-infused and water-infused rats lost weight during their confinement in the restraining cage, the difference in weight loss between them is not significant ($F = 1.32$, $P > .25$). Water infusion leads to an 8.1 percent weight loss

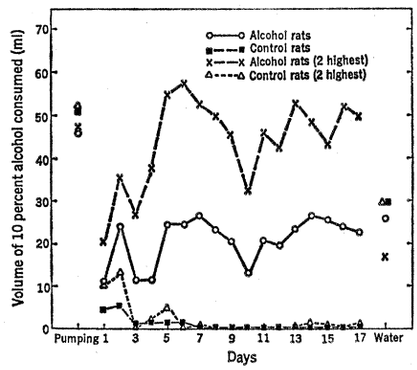

Fig. 1. During the period marked "Pumping" the rats were subjected to a passive infusion of fluid into the stomach; the control rats were pumped with water while the experimental animals were pumped with an alcohol solution (10 percent by volume). Pumping was then stopped and both groups were given a choice between water and the alcohol solution while on unlimited food. The points above "Water" indicate the average intake of water for each group over the whole period.