events involving them suffer from the same discouraging limitations as analogous processes with RNA. And, of course, we are still left with the problem of ribonucleotide synthesis. Could the ancestor of RNA have folded into catalysts that generate β-D-ribonucleotides? Many details remain unclear.

Perhaps the most significant implication of the new work is that it demonstrates a link between informational polymers of contemporary organisms and those previously considered to be inappropriate for prebiotic studies, thereby greatly expanding the repertoire for re-enacting life's beginnings. Suddenly, the gap between the anti-RNA conditions on the primitive Earth and the RNA world does not appear so forbiddingly wide. □

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NEUROPSYCHOLOGY

Is dopamine a missing link?

Robert Desimone

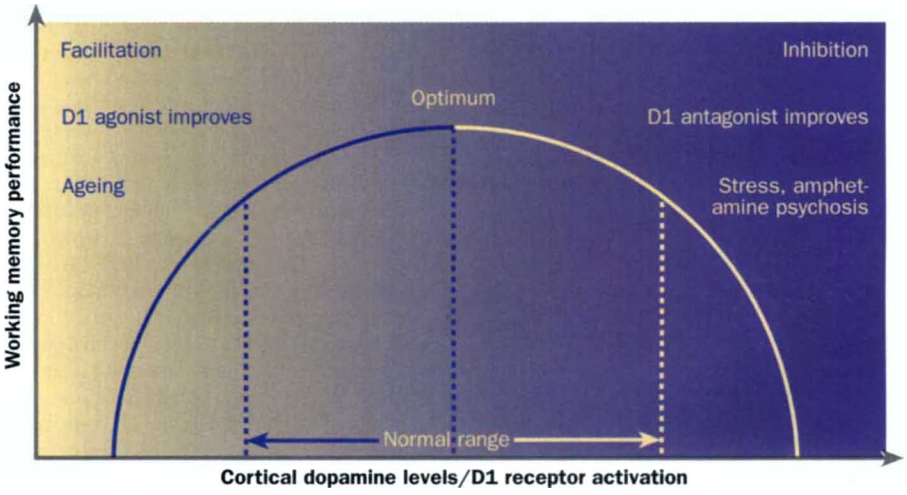
THE ability to grab a fleeting item of information coming through our sensory systems and to hold it on-line for a few seconds while we plan a response is one of the defining features of working memory. Work in non-human primates indicates that this aspect of working memory is mediated, at least in part, by 'voluntarily' maintaining the neuronal response to a stimulus for up to many seconds after the stimulus is no longer present. In a paper on page 572 of this issue, Williams and Goldman-Rakic[1] now show from combined physiological recording and iontophoresis of drugs into monkey prefrontal cortex that this deceptively simple mnemonic process is regulated by the D1 dopamine receptor. This provides a potential mechanistic link between four of the most commonly associated subjects in mental health research, namely, prefrontal cortex, working memory, dopamine and neuropsychiatric disorders.

The notion of working memory comes from human cognitive psychology, where it encompasses a variety of interrelated cognitive phenomena and concepts, including covert articulation or rehearsal of verbal material, visual imagery, active short-term memory, and the actions of a 'central executive' that coordinates and plans behaviour and participates in problem solving[2]. All of these processes involving the maintenance and manipulation of information are distinguished by the fact that they seem to be under voluntary, conscious and effortful control. Considering that working memory is integral to cognition in general, it is not surprising that it is disturbed in many neuropsychiatric disorders, such as schizophrenia. The dopaminergic system has been implicated in several such disorders, and pharmacological treatments involving the dopaminergic system are known to affect working memory in both normal people and psychiatric patients. Brain-imaging studies measuring cerebral blood flow have shown that prefrontal areas are selectively activated when normal people perform tasks requiring working memory, and this prefrontal activation seems to be abnormal in patients with schizophrenia[3].

The physiological evidence for working memory in animals has typically come from studies in which animals are given a brief cue to hold in memory during a delay period of a few seconds and are then required to make some choice or response based on this cue. More than two decades ago physiological studies in monkeys found that neurons in prefrontal cortex become activated during the delay period of such a task[4,5], with different neurons showing different levels of activity depending on the cue[6]. That is, prefrontal cells seem to maintain a representation of the cue during the delay. This delay activity seems to be under the monkey's voluntary control, as it occurs only for stimuli that the monkey is required to remember and terminates as soon as the memory is no longer required. Since then, studies have shown comparable delay activity in premotor cortex, parietal cortex, visual cortex and several subcortical structures including the striatum, with the anatomical locus of the effects depending on the type of information represented[7]. Despite the widespread distribution of cells with such properties, prefrontal cortex may be a critical site or even one of the originators of the signals that activate cells in other areas. In inferior temporal cortex, for example, delay activity is disrupted whenever the animal processes intervening sensory inputs, whereas it is maintained in prefrontal cortex as long as the animal is able to maintain the memory of the cue[8,9]. Furthermore, local cooling of prefrontal cortex greatly diminishes delay activity of neurons in posterior parietal cortex during spatial working memory tasks[10].

In their new study, Williams and Goldman-Rakic used a spatial delayed response task, in which the monkey was trained to remember the location of a cue flashed on a screen and to make an eye movement to that location after a delay period. Some cells in prefrontal cortex were activated by the cue and maintained their activity during the delay, but only when the cue location fell within a certain portion of the screen, which is termed the 'memory field' of the cell. When the authors iontophoresed an antagonist of the D1 dopamine receptor at low currents, the delay activity was enhanced only for cues presented in the memory field of the cell; no other aspect of the cell's firing rate was changed. Thus, the signal-to-noise ratio of the cell was increased by the D1 blocker, just for the mnemonic information in the task.

This was a very surprising result, as it had previously been shown that D1 antagonists injected either systemically or directly into the prefrontal cortex actually impaired the behavioural performance on a working-memory task[11]. An explanation emerged when Williams and Goldman-



An inverted 'U'-shaped function for the role of the dopamine D1 receptor in prefrontal mechanisms for working memory. When either prefrontal dopamine levels or D1 activity are below the optimal range, as may occur with ageing, or above the optimal range, as may occur in stress and amphetamine psychosis, working memory performance is impaired. In such instances, D1 agonists or antagonists, respectively, may restore performance to the optimal range.

Rakic tried higher injection currents: the higher concentration of the antagonist nonspecifically inhibited the firing of the cells. They found the same nonspecific inhibition on injecting any amount of a D2 antagonist. The regulation of prefrontal activity by dopamine is thus more complex than could have possibly been imagined. The exquisite sensitivity of cells both to the magnitude of the receptor occupancy and to the specific dopamine receptor contacted would explain why alterations in either the amount of dopamine in the synapse or in the activity in one of the receptors so often lead to working memory impairments. Conversely, the results open the possibility for improving working memory function through carefully balanced receptor manipulations.

Is the D1 receptor the tie that binds together working memory, prefrontal cortex and neuropsychiatric disease such as schizophrenia? If so, there must be many other links in the chain. Typical neuroleptic drugs that improve schizophrenic symptoms work primarily through the D2 receptor, not the D1, and the more recently developed atypical antipsychotic drugs have much more affinity for a subtype of 5-HT (serotonin) receptor than for either D1 or D2 receptors[12].

Probably the safest answer to the question at this point is that the dopaminergic system does not work in isolation in the cortex but rather interacts in a complex fashion with other modulatory systems. These interactions will have to be worked out at the physiological, pharmacological and behavioural levels, using the delayed response task and other tasks in monkeys that tap some of the more complex aspects of human working memory. Indeed, one of the most exciting aspects of the study by Williams and Goldman-Rakic is that single-cell physiology and pharmacology can now actually be accomplished in awake monkeys performing tasks that engage cognition. □

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NUCLEAR STRUCTURE

Gadolinium peanuts

P. J. Twin

THE recent observation of γ-rays characteristic of a hyperdeformed or 'peanut-shaped' nucleus in the rare-earth element gadolinium-147 has excited nuclear structure physicists. The experiment, reported in *Physical Review Letters*[1], was carried out by a collaboration working on the large multi-detector γ-ray array Gammasphere at the Lawrence Berkeley Laboratory in California.

Nuclei have a spherical or slightly prolate deformation in their ground state, but much larger deformations become energetically possible in some nuclei as they rotate at large angular momenta. Superdeformed nuclei (in which the major axis is twice the minor, see Fig. 1) were first observed[2] nearly ten years ago and studies of the properties of these nuclei[3,4] have revealed many new phenomena and insights into the structure of nuclei. Calculations[5] that predicted the existence of superdeformed shapes have been further developed to explain these features. These calculations also predict that at very high spins with angular momentum around $80\hbar$ (beyond the normal fission limit), the hyperdeformed shape (major:minor axis ratio = 3:1) becomes energetically favourable in nuclei with certain numbers of protons and neutrons. The inclusion of octupole (pear-shaped) correlations[6] produces an asymmetry in the shape rather like a peanut for nuclei around atomic number $A=150$ (Fig. 1).

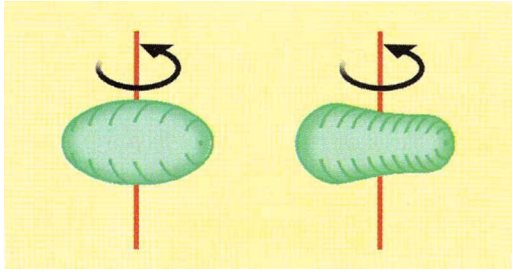

FIG. 1 Schematic of superdeformed (left) and hyperdeformed (right) nuclear shapes.

The initial signal of a hyperdeformed nucleus is a γ-ray sequence in which the energy difference between successive γ-ray transitions should be constant at about 30 keV, compared with a value of about 50 keV for superdeformed shapes. Scientists have scanned their data sets in superdeformed experiments but in only one case was there any indication of a positive signal, when a group from Chalk River Laboratories found tentative evidence[7] for such a sequence in dysprosium-153. These nuclei were formed using a slightly different reaction, as a proton (in addition to the usual several neutrons) was emitted from the compound nucleus before the γ-ray cascades. The experiment involved detecting the protons in a compact, efficient array, as well as the main γ-ray instrument.

In the past couple of years two very efficient γ-ray instruments, Gammasphere and Eurogam, have been built[8]. Gammasphere has been operated with the microball, a compact array of detectors which can efficiently detect and identify protons, α-particles and other light ions. It was this combination of instruments that produced the new evidence for hyperdeformation — two sequences of respectively 9 and 11 discrete γ-rays, each with energy separations close to 30 keV (as shown in Fig. 2).

Gadolinium-147 nuclei constitute only about 5 per cent of the products of the reaction of 230 MeV vanadium-51 with a molybdenum-100 target. The proposed hyperdeformed bands are populated at the 0.3 per cent level in gadolinium-147 and therefore the combination of microball and Gammasphere is operating very close to its observational limit in observing these very weak γ-rays. The bands have the expected constant intensity over most of the sequence, decreasing at the highest transition energies. Although the average energy difference between γ-rays is 30 keV, individual values vary irregularly from 25 to 32 keV (with uncertainties of the order of 2–3 keV) and so, rather surprisingly, they are not as constant or smoothly varying as the separations in superdeformed bands.

No spin assignments can be unambiguously made to the hyperdeformed states as the γ-ray sequences have not been linked to known spin states, a situation that still prevails for superdeformed bands. But theoretical predictions are that the nucleus should behave like a rigid body, in which case the γ-ray energies indicate that the sequences would cover the extremely high spin range from about $65\hbar$ to about $90\hbar$. In comparison, the intensities of states in superdeformed bands drop rapidly above $60\hbar$ and none has been observed above $70\hbar$. This rapid decline is not caused by a lack of angular

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