Our results and those of other investigators (*8*, *12*) suggest that educators in the sciences should not treat students as merely lacking the correct information. Instead, educators should take into account the fact that many students have strong preconceptions and misconceptions (*8*) and problem-solving strategies that are different from those used by experts (*12*). When a student's naïve beliefs are not addressed, instruction may only serve to provide the student (as, for example, our subject who spoke of angular momentum) with new terminology for expressing his erroneous beliefs.

The Aristotelian view of motion, that an object remains in motion only so long as it is in contact with a mover, historically preceded the impetus theory. It has been described as the most natural way to conceptualize motion (*5*). Why, then, did our subjects evidence beliefs that echo medieval thinking rather than Aristotelian concepts?

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References and Notes

1. Indeed, the history of science suggests that the principle of inertia is not easily developed on the basis of experience with the world. A coherent statement of this principle was not made until the 17th century.
2. J. Piaget [*The Grasp of Consciousness* (Harvard Univ. Press, Cambridge, 1976)] presented children with a situation similar to that described in our problem 4. The children were given a ball attached to a string and were asked to swing the ball in a circle with the string. They were then to release the string so that the ball would hit a target. Piaget was concerned with the relation between what the children did in attempting to hit the target and what they said they did. However, he mentioned that in describing the behavior of the ball even the youngest child said that it followed a straight line when the string was released. Of course, unlike the subjects' reports in our experiment, the children's descriptions of the ball's behavior were based on observation of the ball. Thus, Piaget's result illustrates the point that it is unlikely that nonveridical perception of situations like those depicted in our problems is the source of our subjects' belief that the balls would follow curved trajectories.
3. J. Larkin, J. McDermott, D. Simon, and H. Simon [C.I.P. No. 408, Carnegie-Mellon University (1979)] suggested that, at least for physics experts, knowledge used in solving textbook physics problems is organized into several different approaches or methods. A person working on a problem adopts a particular approach and attempts to solve the problem by applying the principles appropriate to that approach. According to this view, our subjects who made sophisticated errors adopted an inappropriate approach (a "forces" approach). Also the knowledge about forces that these subjects applied included misconceptions about centrifugal force. As a result, the subjects arrived at incorrect answers to the problem.
4. We are suggesting that people, through their experience with the physical world, develop naïve theories of motion which they use to predict and explain the actions of others.
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10. J. Piaget [*The Child's Conception of Movement and Speed* (Routledge & Kegan Paul, London, 1970); *The Child's Conception of Physical Causality* (Kegan Paul, Trench, Trubner, London, 1930)] explored children's immature conceptions of various aspects of physical reality. Further, in several studies to which our research appears similar, Piaget and his colleagues [B. Inhelder and J. Piaget, *The Growth of Logical Thinking* (Basic Books, New York, 1958)] examined children's approaches to some simple mechanics problems (for example, what determines the period of a pendulum's oscillation?). However, in these studies Piaget was primarily concerned with characterizing the reasoning processes children use in attempting to solve problems. Physics problems were chosen merely as a convenient vehicle for studying these problem-solving processes. Consequently, little attention was paid to the content of the children's preconceptions.
11. D. Norman [*Cognit. Sci.* **4**, 1 (1980)] expresses a similar view in stating that characterizing the nature and content of belief systems should be a major current goal of cognitive science.
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Neurochemical and Behavioral Evidence for a Selective Presynaptic Dopamine Receptor Agonist

Abstract. *A new dopamine analog, 6,7-dihydroxy-2-dimethylaminotetralin (TL-99), was compared to apomorphine in three tests of dopaminergic function in the central nervous system. The tests, performed on rats, included production of changes in locomotor activity (involving both presynaptic and postsynaptic receptors), inhibition of dopa accumulation (quantifying presynaptic receptor activity), and the rotation model (quantifying postsynaptic receptor activation). Apomorphine was efficacious at both presynaptic and postsynaptic receptors, whereas TL-99 was much more efficacious at the presynaptic receptor. This result indicates not only that differences exist between presynaptic and postsynaptic dopamine receptors, but also that these differences may be exploited in the design of selective dopamine agonists.*

Pharmacological research is focused on developing drugs that selectively alter neurotransmission in specific dopamine pathways (mesolimbic, mesocortical, tuberoinfundibular, or nigrostriatal) or that selectively interact with specific types of dopamine receptors (soma-dendritic, presynaptic, or postsynaptic) (*1*). Each dopamine receptor has a characteristic function in the brain, with soma-dendritic receptors controlling dopaminergic neuronal activity, presynaptic receptors inhibiting the synthesis and release of dopamine, and postsynaptic receptors mediating the normal physiological response to dopamine characteristic of the particular brain region.

Identification of a drug that selectively activates one subpopulation of dopamine

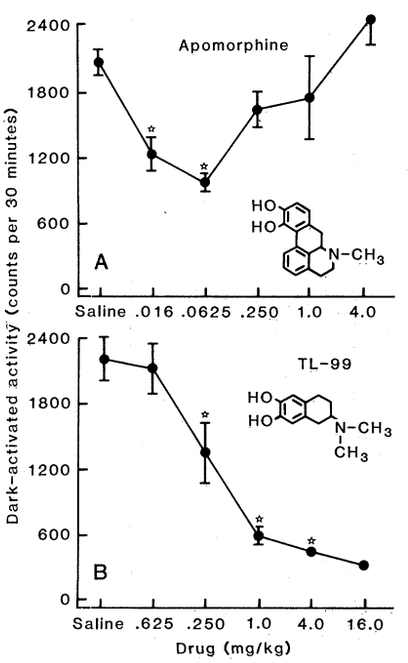

Fig. 1. Comparison of the dose-response curves for apomorphine and TL-99 during dark-activated activity. After 48 hours of exposure to continuous light, two rats were given subcutaneous injections of saline, apomorphine, or TL-99. Five minutes later both rats were placed in a clear Plexiglas cage (14.5 by 50 by 20 cm) on top of an Automex activity meter. The lights were turned off, and activity was determined for 30 minutes by movements of the rats through an electromagnetic field. Two rats were placed in each cage to stimulate each other and therefore raise control activity. Solid circles represent the means, and the vertical lines denote 1 standard error as determined in five groups of two rats. At 16.0 mg/kg, there was only enough TL-99 for one group of two rats. Asterisks indicate a significant decrease ($P < .05$, one-way analysis of variance with least-significant-difference test; two-tailed analysis).

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receptors would have potential therapeutic value, depending on the specific receptor it activates. Thus, a drug that primarily activates postsynaptic dopamine receptors would be indicated in diseases where too little dopamine is being released, as in Parkinson's disease and hyperprolactinemic syndromes (*2*). A presynaptic dopamine agonist would be useful in diseases where too much dopamine is released, as in schizophrenia, Huntington's chorea, and hyperkinetic disorders (*3–5*).

Despite the biochemical heterogeneity of brain dopamine receptors, extensive pharmacological studies have yielded only a few agents that have selective actions (*6*). Tests for assessing activity of central dopamine receptors have included appearance of gnawing, stereotyped behavior, hyperactivity, adenylate cyclase activation, inhibition of prolactin secretion, hypothermia, pecking (in pigeons), rotation (in rats), emesis (in dogs), and more recently, radioreceptor binding techniques (*7–10*). Our tests for assessing central dopaminergic activity in rats include modulation of locomotor activity, inhibition of dihydroxyphenylalanine (dopa) accumulation, and the rotation model. Applying these tests to a series of aminotetralin derivatives, we were successful in identifying 6,7-dihydroxy-2-dimethylaminotetralin hydrobromide (TL-99) as a selective presynaptic dopamine receptor agonist.

Our first in vivo test was modulation of locomotor activity; after rats were made hyperactive by prior exposure to constant light, we measured their locomotor activity in the dark. Low doses of apomorphine had a sedative effect, and higher doses had a stimulant effect (Fig. 1A); this biphasic effect on locomotor activity is consistent with previous observations on apomorphine (*11*). According to current theory on the neurochemical basis for these behaviors, the sedation indicates activation of presynaptic dopamine receptors, and the stimulated activity at higher doses indicates activation of postsynaptic dopamine receptors. Alternative explanations are also possible, such as sedation being mediated by postsynaptic mesocortical dopamine receptors and stimulated activity being mediated by mesolimbic dopamine receptors in the nucleus accumbens (*12*). In contrast to the biphasic effect of apomorphine on locomotor activity, the administration of TL-99 produced a monophasic decline in locomotor activity (Fig. 1B). The sedation induced by TL-99 was dose related, no increase in locomotor activity being displayed with doses as high as 16 mg/kg. Thus TL-99 lacks the postsynaptically mediated stereotyped behavior seen with apomorphine and appears to activate only presynaptic dopamine receptors in the central nervous system (CNS).

In our second in vivo test, we confirmed the presynaptic receptor efficacy of these two dopamine agonists in the CNS by the dopa accumulation method (*13*). Both apomorphine and TL-99 decreased the accumulation of corpus striatal dopa in a dose-related manner (Fig. 2A). Since our assay requires preliminary treatment with γ-butyrolactone, the inhibition of dopa accumulation by these two compounds is probably not mediated by either the soma-dendritic or postsynaptic dopamine receptors (*14*). Thus the dose-related decreases of dopa represent presynaptic receptor activation by both apomorphine and TL-99.

The third in vivo assay consisted of detecting direct postsynaptic dopaminergic agonists within the CNS by means of the rotation model (*15*). Apomorphine produced a dose-related increase in circling behavior, with a maximum response of 535 turns per hour (Fig. 2B). The administration of even low doses of apomorphine (16 and 62.5 μg/kg) induced a significant increase in contralateral circling behavior. In sharp contrast, TL-99 at 4.0 mg/kg induced only a moderate increase of 44 turns per hour. Thus apomorphine is much more efficacious than TL-99 as a stimulant of postsynaptic dopamine receptors in the CNS. The greater efficacy of TL-99 on presynaptic CNS dopaminergic receptors as compared to that on postsynaptic receptors explains the monophasic sedation initially observed in our locomotor activity studies. Therefore, TL-99 represents the first dopamine agonist to be characterized as a preferential stimulant of presynaptic receptors within the CNS.

In the CNS, TL-99 has been reported to be inactive both on stereotyped behavior after systemic administration and on adenylate cyclase activity in vitro (*10*). Furthermore, TL-99 elicits only minimal amounts of hyperactivity and stereotyped behavior after it is injected directly into the nucleus accumbens and caudate nucleus (*9, 16*). These data indicate that TL-99 has little intrinsic affinity for the postsynaptic dopamine receptor; however, further studies are necessary to further exclude such factors as limited access to receptors or activation of dopamine receptors outside of the regions studied so far.

The identification of TL-99 and other dopamine analogs as selective presynaptic receptor stimulants has important clinical implications for various disease

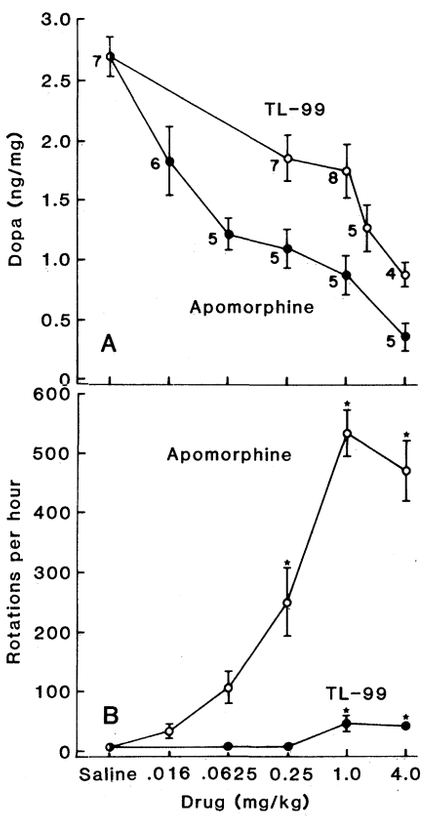

Fig. 2. (A) Neurochemical effect of apomorphine and TL-99 on dopa accumulation in the corpus striatum. Saline, apomorphine, or TL-99 was injected 5 minutes before an intraperitoneal injection of γ-butyrolactone (750 mg/kg) followed 5 minutes later by administration of NSD 1015 [for additional methods, see (*14*)]. The amount of dopa contained in two combined corpus striatal tissue punches is indicated on the ordinate, and the doses of saline, apomorphine, or TL-99 tested are indicated on the abscissa. The symbols represent the means, and the vertical lines denote one standard error for the number of samples indicated to the left of each symbol. All doses of apomorphine and TL-99 significantly decreased dopa accumulation ($P < .01$), by one-way analysis of variance and the least significant difference test (two-tailed). (B) Contralateral rotations induced by apomorphine and TL-99 in rats with unilateral nigrostriatal lesions. Lesions of the nigrostriatal pathway were made by injecting 6 μg of 6-hydroxydopamine hydrobromide in 2 μl of sterile saline containing ascorbic acid (0.2 μg/μl) and infused at a rate of 1.0 μl/min (*8*). The coordinates for injection were anterior from lambda 2.4, lateral 1.8, and vertical from dura 7.0, according to the atlas of König and Klippel (*20*). The number of rotations per hour as indicated on the ordinate was quantified by means of an automatic rotameter. Symbols represent the mean, and the vertical lines denote one standard error of the mean for five rats. Five rats that were given TL-99 subcutaneously at 16.0 mg/kg (not indicated on the abscissa) had 4.25 ± 3.93 turns per hour. Asterisks indicate significant differences from control values ($P < .01$ as determined by one-way analysis of variance and the least significant difference test).

states, especially since the identification of a peripheral dopamine receptor-blocking agent, domperidone, which eliminates emetic and other peripheral side effects of dopamine agonists (*17*). Schizophrenia has recently been found to be dramatically improved by the administration of low, sedative doses of apomorphine (*18*). Since the underlying neurochemical defect of schizophrenia has been viewed as overactivity of dopamine neurons, apomorphine may exert its therapeutic action through presynaptic inhibition of dopaminergic neurotransmission. Therefore, as a selective presynaptic dopamine receptor agonist, TL-99 provides a pharmacologically unique alternative to classical neuroleptic therapy not only of schizophrenia, but also of other disease states, such as Huntington's chorea (*5*), hyperkinetic disorders (*4*), and tardive dyskinesias (*19*) where dopaminergic neuronal hyperactivity is the pathophysiological alteration.

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Electrophysiological Correlates of Ethanol-Induced Sedation in Differentially Sensitive Lines of Mice

Abstract. *Acute electrophysiological effects of ethanol were studied in two lines of mice that differ markedly in their response to the soporific effects of systemic alcohol administration. Cerebellar Purkinje neurons from the genetic line that had long sleep times were one to two orders of magnitude more sensitive to the depressant effects of locally administered ethanol than those from the line that had short sleep times. The data suggest that there are genetically determined specificities in the acute effects of ethanol on central neurons and that such specificities might be used to determine which regions of the cerebellum participate in differences in behavioral responses to this substance.*

Among promising developments in analyzing acute effects of ethanol has been the selective breeding of mouse lines that differ markedly in sensitivity to the soporific effects of this drug. A given dose of ethanol produces a 25-fold longer sleep time in mice that have long sleep times (LS mice) than in those with short sleep times (SS mice) (*1*, *2*), as measured by the disappearance and return of the righting reflex. The rate of disappearance of ethanol from blood is identical in the two lines, and the alcohol content of the blood is much higher for SS mice than for LS mice at their respective times of awakening; this suggests a differential central nervous system sensitivity to the depressant effects of alcohol.

The cerebellum has been implicated in acute central nervous effects of ethanol both electrophysiologically (*3*, *4*) and behaviorally (*4*-*6*). We report here that cerebellar Purkinje neurons in LS mice show a much greater sensitivity to the depressant effects of ethanol than those in SS mice (*7*).

For these in situ experiments, mice were anesthetized with urethan and prepared for recording as previously described (*8*). Spontaneous discharge of Purkinje neurons, identified by their characteristic pattern of single and complex spikes, were recorded by use of multibarreled micropipettes (*9*). Ethanol was administered locally by pressure ejection from an adjacent barrel of the micropipette; release of substances from such pipettes is linearly related to ejection time and pressure (*10*). Effects of alcohol were considered reliable only if they could be obtained at least twice, with recovery of control values in each case. Rate-meter records of electrophysiological changes were quantitated with a digitizing tablet and computer (*11*).

The most striking finding in this study was the marked difference in sensitivity of cerebellar Purkinje cells to ethanol in the different lines of mice (Fig. 1). For each of the 87 neurons suitable for analysis and shown in the bar graph, we se-

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