It's heads they win, tails I lose!

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Keith and Rudy's critical discussion of recent experiments that have been carried out to investigate the behavioral effects of NMDA antagonists is a valuable contribution to current debate about whether or not the underlying neural mechanisms of one type of hippocampal long-term potentiation (LTP) might play a role in certain kinds of learning. In reply, however, I am bound to say that none of their three main points is original, each one having been the subject of constructive discussion and pertinent experimentation among active researchers in the field for the past 2 years. Furthermore, while sharing some of their disquiet about the interpretation of experiments in which channel-blocking noncompetitive antagonists such as MK-801 have been used, I have some difficulty in responding to their other two main points. According to Keith and Rudy (hereafter K-R), where learning *does* occur in the presence of a competitive antagonist (such as AP5), the hypothesis that the mechanisms underlying LTP play a role in that type of learning should be rejected. However, where learning *fails* to occur (or is impaired), the hypothesis can *also* be rejected because sensorimotor side effects of the drug are probably responsible for the impairment. So it's heads they win, tails I lose! I shall endeavor to undermine such a cunning attack by arguing that the coin of LTP's destiny as a phenomenon of functional significance is still spinning in midair, its fate uncertain. Of course, these are matters too important to be decided on the toss of a coin, or to deserve so hasty a rejection as K-R heap upon it; a more cautious assessment of available data is essential.

Among their specific comments on the Morris, Anderson, Lynch, and Baudry (1986) study, K-R imply that I and my colleagues misinterpreted the results because the dissociation between place navigation and visual discrimination learning was confounded with a change in intertrial interval (ITI), and that detectable place learning did occur during the brief period of training when the ITI was the same 30 sec as was used in the visual discrimination control task. Second, they suggest that the apparent impairment over the early training trials was due to a sensorimotor impairment. Third, they point out that AP5 has

other effects upon hippocampal physiology than just the blockade of LTP and that these could equally be the cause of any learning impairment observed. And fourth, they indicate that other more appropriate control procedures could have been used than the single but "faulty" one we did include. These points will be considered in turn.

Does Learning Occur in the Presence of a Competitive NMDA Antagonist?

The 1986 study included behavioral data from three separate training phases of a place navigation water maze task (training, further training, reversal) and also data from a transfer test. The D,L-AP5-treated rats were significantly impaired relative to L-AP5 and placebo controls in each comparison. It is nevertheless true that performance by all groups toward the end of the eight additional training trials after the transfer test, conducted at an ITI of 30 sec, was better than that shown on the first trial of the reversal phase which began the next day. Thus, the D,L-AP5-treated rats may have learned something about the location of the platform during at least one phase of training. Largely on the basis of this single result, K-R conclude that "the central finding" of Morris et al.'s (1986) study is that "AP5-treated animals displayed place learning." I beg to differ.

First, the further training phase in which the D,L-AP5 group is claimed by K-R to have displayed place learning was actually the one in which they showed the most significant impairment relative to both L-AP5 and control groups ($p < .0005$). Second, although the increase in latency between the end of further training and the start of reversal training failed to reveal significant differences between groups, there was nevertheless a trend toward a smaller increase in the D,L-AP5 group ($.10 > p > .05$). Taken together, these results imply that if the D,L-AP5 learned anything about the platform's location, it was certainly less than that shown by the other groups. However, finding less learning is not good enough for K-R, who go on to suggest, uncritically in my view, that for the NMDA-receptor-dependent learning hypothesis to be true, D,L-AP5-treated rats should behave like hippocampally lesioned rats in a reversal test (see, e.g., Sutherland, Whishaw, & Kolb, 1983). There are two problems with this argument. First, rats with ibotenate lesions restricted to the hippocampus (i.e., lesions damaging all of the hippocampus [24 injection sites] but sparing the subiculum and extrahippocampal structures) do learn something about a platform's location (Morris, Schenk, Tweedie, & Jarrard, 1990). Second, why should a drug, one of whose effects is to block associative LTP in the dentate gyrus and area CA1, reproduce every impairment displayed by hippocampally lesioned rats? Leaving aside the other effects of the drug for the time being, there are surely grounds for predicting that blockade of this form of LTP might reproduce only a subset of the impairments

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caused even by neurotoxic lesions. Perhaps AP5 causes only an impairment in the rate of place navigation learning, rather than its asymptotic level. In summary, one should not read too much into a single ambiguous measure of performance which indicates that some place learning might have occurred in the D,L-AP5 group in the face of five other measures which show that this group's performance was severely impaired.

A final point, as mentioned by K-R, is that it must be remembered that the rats on whom behavioral tests were conducted were different rats from those in whom LTP was examined. Thus, some of the D,L-AP5 behavioral group may have had a lower interstitial AP5 concentration than is necessary to block LTP completely (the companion electrophysiological study gave a group average of -6.3% LTP, but some individuals showed partial LTP above the group mean, while others were below it). To appeal to this point is not quite the appeal to irrefutability that K-R imply (see their final paragraph and Note 3), since "negative" LTP is possible while negative escape latencies are not. I shall return to the obvious need for within-animal dose-response studies of both learning and LTP *in vivo* later on.

Dissociating the Learning Impairment from Sensorimotor Side Effects

K-R refer to Mondadori, Weiskrantz, Buerki, Petschke, and Fagg (1989) in drawing attention to sensorimotor impairments sometimes induced by NMDA antagonists. In fact, attention to this issue's relevance to studies of learning predates Mondadori et al.'s paper. In April of 1988, I gave a paper at the Royal Institution in London, in which I discussed the importance of the learning/performance distinction (see Morris, 1988, p. 298) and presented two of several experiments in which I and my colleagues had attempted to dissociate the AP5-induced learning impairment from certain sensorimotor side effects (p. 301 ff.). The problem I was trying to grapple with is that there are NMDA receptors in many parts of the central nervous system that could, presumably, subserve a variety of different psychological functions. It follows that to use NMDA antagonists to investigate the role of hippocampal LTP in learning is to run the risk of incurring numerous unwanted "side effects" (such as those cited by K-R). Necessarily, their presence complicates the interpretation of experiments on learning and may even, as K-R suggest, be causally responsible for the "apparent" learning impairments. With respect to this problem, I can only plead that no sooner were I and my colleagues aware of it than we began conducting what we hope are pertinent experiments addressing it, and that these experiments have continued for over 3 years.

Concerned that some D,L-AP5-treated rats fall off the escape platform during the 1st day of spatial training (and normal rats do this too), I conducted a study in which some rats received nonspatial pretraining before either the minipumps were implanted or spatial training commenced, and in which this aberrant platform behavior was filmed with

a second video camera and scored independently (see Morris, 1988, and 1989, Experiment 3). The results showed that pretraining caused a striking reduction in the probability of this sensorimotor disturbance, but that it had no effect on the magnitude of the AP5-induced spatial learning impairment (the *F* ratio for the interaction term was less than 1). K-R do not cite this study, nor do they refer to another experiment addressing the issue of anatomical specificity, in which intrahippocampal infusions of nanomolar quantities of D,L-AP5 were shown to impair spatial learning, provided a dose sufficient to block LTP was administered (presented at the Society for Neuroscience in 1987 and published as Morris, Halliwell, & Bowery, 1989). An important feature of the latter study was the use of quantitative autoradiography and radio-labeled compounds closely related to AP5, to establish whether the intended local drug infusion did, in practice, restrict drug diffusion to the hippocampus (except for escape in the region of the cannula track, it did). In a further study reported to the Society for Neuroscience last year, Butcher, Hendry, and Morris (1989) have shown that rats given intraventricular infusions of D-AP5 at a dose that we know (see below) blocks LTP *in vivo* can simultaneously retrieve spatial information acquired prior to minipump implantation as efficiently as artificial CSF controls and be impaired in learning a new spatial location relative to controls. These results imply that AP5 is probably not affecting the acuity of vision, particularly for distal extramaze cues, because the sight of these cues is equally necessary for retrieval of old information as it is for processing new information.

Although these experiments constitute part of our efforts to address the sensorimotor disturbance problem, K-R may take the view that they are "not convincing." No, they are not, but I hope K-R will concede that they are at least a step in the right direction! In fact, the issue of sensorimotor disturbance is part of a much wider and deeper issue about what NMDA receptors are doing in different parts of the nervous system. To discuss this takes us outside the realm of experimental psychology, but a few comments may be apposite. It is important to appreciate that NMDA receptors are *not* "learning receptors." Their function cannot be adequately described in psychological terms—the appropriate level of discourse being pharmacological. NMDA receptors are a molecular device for detecting the conjunction of presynaptic activity and postsynaptic depolarization, and for signaling this detection by means of a different ionic signal (namely Ca^{2+}) from that used ordinarily to mediate fast epsps (i.e., Na^+). While this pharmacological property is potentially relevant to the psychological processes of associative learning, such as the detection of contiguity, it is important to appreciate that "detection" is not the same as "representation." Thus, although activation of NMDA receptors may help us understand aspects of associative learning (e.g., how the nervous system detects that one stimulus occurs in association with another), a fuller understanding will depend critically on how stimulus information is

represented neurally and into what circuitry these receptors are embedded (see McNaughton, 1989). In other circuits and at different stages of development, NMDA receptors perform a myriad of different functional roles through this same pharmacological property. Thus, activation of NMDA receptors during development seems to play a role in experience-dependent self-organization (Cline, Debski, & Constantine-Patton, 1987; Kleinschmidt, Bear, & Singer, 1987; Singer, 1990), whereas, in the adult spinal cord, their activation is involved in the integration of suprasegmental reflexes (Davies & Watkins, 1983). In *Xenopus* embryos, activation of NMDA receptors provides a convenient way of turning on a Ca^{2+} -dependent K^+ current that repolarizes neurons and thus stabilizes the rhythmic activation characteristic of swimming (see Dale, 1989). In short, blockade of NMDA receptors is bound to have a multiplicity of effects, and great care must be exercised in experiments on learning to achieve both behavioral and anatomical specificity, and in controlling dose.

Does AP5 Have Other Effects on Hippocampal Electrophysiology Than Merely Blocking LTP?

K-R cite Leung and Desborough's (1988) study, in which intraventricular infusions of AP5 substantially reduced the power of atropine-sensitive hippocampal RSA (or "theta"). I note that K-R share the anxieties I have already expressed elsewhere about the implications of this study (see Morris, 1989, p. 3053). Specifically, Winson (1978) has shown that disruption to hippocampal RSA can cause a spatial learning impairment. Thus, if AP5 blocks both RSA and LTP, the AP5-induced place navigation impairment might be caused by the RSA blockade rather than the LTP blockade. It should be noted, however, that in Leung and Desborough's (1988) study, the reduction in hippocampal RSA was only apparent at the highest dose, when 100 nm of AP5 was infused over 3 min—a rate of infusion over 60 times faster than our 20 nm/h chronic infusion protocol. Furthermore, they reported that at this dose, their animals became "ataxic and assumed an unsteady gait with the abdomen held near the floor during walking." Such behavior has never been seen in our animals chronically treated with AP5 at doses sufficient to block LTP (and only rarely at higher doses). Of course, comparisons between local and chronic infusion protocols are fraught at the best of times, so we did a pilot study to examine hippocampal RSA in 2 rats subject to chronic infusion of 30-mM D-AP5. No changes in RSA were observed (see also Whishaw & Auer, 1989, p. 504). Although we in no way doubt Leung and Desborough's (1988) findings, a more comprehensive study of the effects of chronic AP5 infusion on hippocampal RSA is underway in my laboratory.

However, once again, the interpretive issues surrounding systemic pharmacological experiments are deeper, and transport us with, I trust, shared delight into new intellectual territory. For in addition to affecting RSA at high doses, NMDA antagonists can cause reductions in hippocampal excitability (Abraham & Mason, 1988; Errington,

Lynch, & Bliss, 1987) and a "truncation" of normal complex-spike firing (Abraham & Kairiss, 1988). These effects may also contribute to the learning impairment. However, they may all be linked with respect to an underlying mechanism, inasmuch as, for example, complex-spike firing may be one way in which the sustained Ca^{2+} transient necessary for triggering LTP occurs "naturally" during learning (Abraham & Kairiss, 1988; see also Lynch, 1986, pp. 43-44). The truncation of complex-spike firing may therefore be a parallel (i.e., nonindependent) change in hippocampal electrophysiology to that of the blockade of LTP. The presence of a competitive NMDA antagonist binding to the receptor recognition site will prevent the associated ionophore opening and thus the Ca^{2+} transient from occurring. The irony that a complicating "side effect" of NMDA receptor blockade might help guide us to identify one of the naturally occurring causal events capable of triggering alterations in synaptic efficacy should not be lost.

The Need for Control Experiments

K-R's concern that appropriate control experiments be run before one concludes that the effects of an NMDA antagonist on performance are due to an effect on learning per se is well taken, and I concede that changing the ITI between the place navigation and visual discrimination experiments of the 1986 study was unfortunate. However, in the absence of explanation, the claim that "the magnitude of the sensorimotor and motivational effects of NMDA receptor antagonists [may] depend on inter-trial interval" is mere speculation. The point of the visual discrimination study was to find out whether or not AP5 had some gross effect on vision or motivation, using a task that we knew to be insensitive to hippocampal lesions (see also Butcher, Hamberger, & Morris, 1990, where Goddard's [1986] anxiety about differential drug diffusion has been addressed). However, since 1986, we have run numerous other AP5 place navigation experiments at a variety of ITIs. Although we do not fully understand the reasons for this, it turns out that a cumulative overnight impairment is found on a reference memory place navigation task run at a 30-sec ITI (e.g., six trials per day), whereas no impairment is obtained in a working memory place navigation task (Morris, 1983, Experiment 2) in which the interval between Trials 1 and 2 is 30 sec (the escape platform being moved to a new location between days). A clue to what might be happening is to be found in Frederickson, Frederickson, and Danscher's (in press) finding that chelation of mossy fiber bouton zinc by the chelator DEDTC does impair the working memory task at a 30-sec ITI.

K-R's further criticism that we should have run a random platform control condition is a different matter. In fact, my colleague Sabrina Davis has run such a condition and found that D-AP5 and aCSF rats do not differ, but that both groups do far worse than either our highest dose fixed platform location D-AP5 rats or rats given either aspiration or ibotenate hippocampal lesions. We are

now skeptical about the value of this control task. The problem centers on the relative sizes of the pool and platform: In Edinburgh, these are 200 and 10 cm in diameter, respectively. This means that the ratio of their surface areas is 400:1, ensuring that the chance of finding the platform is very low. Although this has the effect of both encouraging a spatial strategy in the main control group and amplifying any subtle differences between the control and experimental groups, it means that rats trained in the random platform condition have a very low chance of finding the platform. Unfortunately, they react to this failure by returning to their initial "strategy" of swimming thigmotactically against the sidewalls of the pool and thereby collect a large number of (maximal) 120-sec latency scores (the mean escape latency in the random control procedure was circa 85 sec). What is required is a procedure in which continued searching throughout the area of the pool is sustained but searching in a specific location prevented. The design of such a procedure eludes us (increasing the size of the platform is one possibility—but then comparability with fixed platform location experimental groups is lost).

Use-Dependency and the Interpretation of Experiments Involving Noncompetitive Antagonists

The main response to K-R's comments concerning learning experiments in which MK-801 has been used is made by Gallagher in this issue of *Psychobiology*, but I would like to add a few points.

The great virtue of MK-801 is that it crosses the blood-brain barrier, so that i.p. injections are possible. But there are at least two major disadvantages. First, an i.p. route of administration will almost certainly give rise to much greater drug access to spinal cord NMDA receptors than the chronic i.c.v. infusion protocol used with AP5. Thus, one runs a greater risk of the rats' displaying disruption of suprasegmental reflexes (Davies & Watkins, 1983; to be fair, I don't know if this assertion is true, because we have never measured spinal cord AP5 levels following i.c.v. infusion). However, and more importantly, MK-801 is a noncompetitive channel-blocking drug that can only gain access to the ionophore when the voltage-dependent Mg^{2+} block is released. It therefore displays "use-dependency" (see Kemp, Foster, & Wong, 1987). The likely reason why MK-801 is such an effective anti-ischemic drug (Iversen et al., 1989) while not blocking LTP very effectively may be the following: Under conditions of sustained glutamate release and/or postsynaptic depolarization, MK-801 will bind to its intrachannel site and thus completely block Ca^{2+} entry (which a competitive antagonist cannot do, precisely because it is competitive), whereas, under conditions of transient glutamate release and/or postsynaptic depolarization, both MK-801 and Ca^{2+} will have access to the channel, and enough Ca^{2+} may enter individual dendritic spines to trigger mechanisms responsible for altering synaptic efficacy before the

channel block has built up (a sufficient dose of a competitive antagonist will completely prevent channel opening under conditions of transient activation). Thus, MK-801 does not block LTP soon after drug injection, but rather requires a period of agonist activation for the channel block to build up.

What are the implications of this point for learning experiments done with MK-801? I fear they are quite complicated. If MK-801 is being used to block hippocampal NMDA receptors sufficiently to block the neural mechanisms underlying LTP, both high doses (circa 0.25 mg/kg) and long injection-testing intervals (circa 2 h) are probably required. As so often in science, the earliest study often hits on the appropriate methodology without one's necessarily realizing why the protocol is so appropriate. Clineschmidt et al. (1982) report that MK-801 impaired the performance of a lick-suppression conflict test with an ED50 of circa 0.25 mg/kg if and only if it was given at least 2 h before testing! But if these strictures are correct, I am left with a conundrum. First, the sensorimotor disturbances induced by MK-801 *in vivo* are seen within 10 min of drug injection. Second, use-dependency *in vivo* may be less apparent than it is *in vitro* (Lodge et al., 1988, p. 247 ff.), largely because of the greater presence of endogenous glutamate *in vivo*. One possibility might be that in areas of the brain that, neurally speaking, are relatively "quiet" (such as area CA1 of the hippocampus), the induction of an MK-801 channel block takes place slowly, whereas, in "noisy" brain areas (such as globus pallidus, where high-frequency firing occurs frequently), a channel block might develop more rapidly. Although there is some difficulty in using this proposal to explain Abraham and Mason's (1988) finding that perforant path stimulation failed to accelerate the induction of channel block, it does have the virtue of pointing to why sensorimotor disturbances are seen much earlier than a blockade of LTP (and it does not require there to be regional differences in the functioning of NMDA receptors). Unfortunately, if true, it presents a further conundrum—namely, how to explain Robinson, Crooks, Shinkman, and Gallagher's (1989) results concerning the effects of MK-801 on place navigation in the water maze. I am frankly at a loss on this point, not least because, as K-R note, Halliwell and Morris (1987) did not obtain behavioral results comparable to those in the admittedly much more thorough experiments of both Robinson et al. (1989) and Whishaw and Auer (1989).

Space does not permit a more detailed assessment of the several intriguing learning experiments that have been done with MK-801. I have criticized Mondadori et al.'s (1989) paper elsewhere and will not repeat the arguments here (Morris, *in press*). However, what is clear is that MK-801's pharmacological mode of action renders it a most interesting drug whose posttrial (Mondadori et al., 1989) and pretrial (Robinson et al., 1989; Whishaw & Auer, 1989) effects are surely worthy of investigation, irrespective of whether the drug blocks LTP. Neverthe-

less, to describe Robinson et al.'s (1989) interpretation as "gratuitous" strikes me as both unfriendly and ill-judged. Experiments rather than insults are the right way to resolve these matters.

Reculer pour mieux sauter

When I moved from a psychology to a pharmacology department in 1986, I and my colleagues felt it would be appropriate to conduct a dose-response study. This was partly to increase our "street-credibility" in the coffee lounge, but, joking aside, it was also because certain problems concerning the effects of AP5 on spatial learning and LTP in vivo can be resolved with reference to their dose-response profile. Accordingly, in a joint project with Sabrina Davis and Steve Butcher, over 60 rats have been put through a detailed protocol in which each animal is subject to nonspatial pretraining, minipump implantation with varying doses of D-AP5, spatial learning, attempted LTP induction, microdialysis of interstitial hippocampal AP5 concentration, and, following sacrifice, whole tissue dissection of various brain areas for AP5 analysis. AP5 concentration is measured using HPLC by means of fluorescence detection. Several pertinent findings have emerged from this study (Morris, Davis, & Butcher, in press). First, a sensorimotor disturbance is induced by AP5, but only at doses well above that required to block hippocampal LTP in vivo. Second, we have been unable to find a dose of D-AP5 that blocks LTP in vivo yet leaves spatial learning unaffected. Parallel dose-response effects are obtained. Third, AP5 is "trapped" in interstitial space by an EGTA-sensitive mechanism such that circa 97% of the whole-tissue AP5 is unavailable to receptors. Thus the ratio of whole-tissue to effective AP5 concentration is circa 30:1. Fourth, if the LTP in vivo and spatial learning performance are normalized in relation to controls and plotted against LTP in vitro or D-AP5 displacement of [³H]-D-AP5 binding in a ligand-binding assay, our results are found to be exactly on top of the LTP in vitro data and, as expected, slightly to the right of the ligand-binding data (AP5 being a competitive antagonist and the binding assay conducted in the absence of L-glutamate). Furthermore, a regression analysis of mean escape latency against effective interstitial AP5 concentration reveals a correlation coefficient of 0.84 (df 55, $p < .001$), thus accounting for 71% of the behavioral variance. In our view, these findings offer little support to those who wish to dismiss the "NMDA-receptor-dependent LTP hypothesis." On the contrary, they offer striking support for the view that activation of hippocampal NMDA receptors is necessary for the induction of at least one type of hippocampal-dependent learning.

Conclusion

In my view, K-R have made too hasty a dismissal of the NMDA-receptor blockade strategy of investigating the role of LTP in learning. Like them, I recognize that systemic pharmacological experiments are fraught with inter-

pretive difficulties. However, their possessive claim that "what has gone unappreciated is that the NMDA-receptor blockade approach . . . would permit one to reject the hypothesis that NMDA-receptor-dependent LTP is a memory mechanism" (p. 252) is puzzling, because it is precisely because of such a possibility that Lynch's, Gallagher's, and my own groups have devoted so much time to conducting relevant experiments. In short, such experiments are worth doing!

Twenty years of research since Bliss and Lomo's original discovery have revealed that hippocampal LTP possesses a number of properties desirable of a memory mechanism, that some of these properties (e.g., decay time-course and saturation) can be usefully exploited in experiments on learning (see Barnes, 1988, for review), and that its blockade by NMDA antagonists does cause a behaviorally selective learning impairment. But the scope is greater yet, for psychobiological research on the role of synaptic plasticity in memory offers the exciting opportunity of making contact with neural network research attacking the problem from a different vantage point (e.g., Crick, 1989; McNaughton, 1989). In this endeavor, we experimentalists have an important responsibility, for there remain many mysteries about the involvement of synaptic plasticity in learning that will only yield to an experimental attack. It is my firm belief that carefully conducted behavioral experiments, in which NMDA antagonists and other new compounds are used as they become available, will continue to play an important part in their resolution.

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