REVIEW

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Milton Keynes MK7 6AA, UK**God's Organism? The Chick
as a Model System for
Memory Studies****Abstract**

The young chick is a powerful model system in which to study the biochemical and morphological processes underlying memory formation. Training chicks on a one trial passive avoidance task results in a molecular cascade in a specific brain region, the intermediate medial hyperstriatum ventrale. This cascade is initiated by glutamate release and engages a series of synaptic transients including increased calcium flux, up-regulation of NMDA-glutamate receptors, membrane protein phosphorylations, and the retrograde messenger NO. Expression of immediate early genes *c-fos* and *c-jun* precedes the synthesis, glycosylation, and redistribution, >4 hr downstream, of a number of synaptic membrane proteins, notably NCAM and L1. Other membrane proteins required in the early phase of memory formation include the amyloid precursor protein (APP) and apolipoprotein E. There are concomitant increases in dendritic spine number and changes in synaptic structure. Nonsynaptic factors, including corticosterone and BDNF, can modulate retention of the avoidance response, enhancing the salience of otherwise weakly retained memory. These results are discussed in relation to general concepts of memory formation and the spatio-temporal distribution of the putative memory trace.

**Early Learning
in the Chick**

The distinguished biochemist Hans Krebs once remarked that God had provided just the right organism with which to study any particular biological problem. The purpose of this review is to argue that the young domestic chick rates high among God's organisms for the study of the molecular and cellular mechanisms of memory formation. Chicks are precocial birds and need actively to explore and learn about their environment from the moment they hatch. Therefore, they learn very rapidly to identify their mother on the basis of visual, olfactory, and auditory cues (imprinting) to distinguish edible from inedible or distasteful food, and to navigate complex routes. Training paradigms that exploit these species-specific tasks work with the grain of the animal's biology and because such learning is a significant event in the young chick's life, the experiences involved may be expected to result in readily measurable brain changes. Chicks have large and well-developed brains and soft unossified skulls, making localized cerebral injections of drugs easy without the use of implanted cannulae or anaesthesia. The virtual lack of any blood-brain barrier in these young animals also ensures rapid entry into the brain of peripherally injected agents. Against these advantages must be weighed the relatively limited knowledge of the intimate neuroanatomy of the avian brain (see Csillag 1999), a degree of genetic heterogeneity, and the complication resulting from the fact that in such young animals task-induced changes in cerebral biochemistry,

electrophysiology, or morphology are superimposed on rapidly developing neural systems (Andrew 1991; Rogers 1995).

Learning Paradigms

The study of both the phenomenology and the neurobiology of learning and memory in avian species has a long and distinguished history. Pigeons vied with rats as the favorite laboratory animals for behaviorists studying conditioning, but more “natural” forms of learning have proved fascinating. Marler, Konishi and Notttebohm pioneered the behavioral and neurobiological analysis of song learning in song sparrows, canaries, and zebra finches (Notttebohm 1970, 1980; Konishi 1989; Marler 1991), tracing neural pathways, and identifying issues of lateralization, and hormonal and related effects that have found their parallels in work with the chick. Krebs, Sherry, and their colleagues explored the role of the hippocampus in food-storing birds such as marsh tits and chickadees (Krebs et al. 1989). More recently some of this work has begun to move to the biochemical and molecular level that I focus on here in the context of the chick. The prospect of using the young chick for the study of cellular and molecular memory mechanisms emerged in the 1960s. Bateson and his colleagues opted for the study of visual imprinting (for review, see Horn 1985). Imprinting, as a form of early learning in some avian species, had been known folklorically for many years (Bateson 1966), but was drawn to scientific attention by the work of Lorenz (e.g., Lorenz 1935), although his interpretations of the phenomenon were not received uncritically. The study of the neurobiology of imprinting has continued in Horn’s and other labs (Johnston and Rogers 1998; McCabe and Nicol 1999). Scheich, Braun, and their colleagues explored auditory imprinting (Scheich 1987; Braun et al. 1999). In these models, chicks are exposed for up to 2 hr to visual or auditory cues that come to represent “mother” (flashing light, stuffed hen, tone). They will subsequently approach the familiar object when offered a choice between it and an unfamiliar stimulus.

Cherkin (1969) developed a one-trial passive avoidance learning task based on the young chick’s tendency to peck at small bright objects such as beads, which is discussed in more detail below. In an appetitive visual discrimination task, the chick learns to distinguish food crumbs scattered on the floor of its pen from rather similar pebbles or beads glued to the surface (Andrew and Rogers 1972; Tiunova et al. 1998). Isolated chicks will quickly learn a simple maze to rejoin their hatchmates (Gilbert et al. 1989; Regolin and Rose 1999). Barber et al. (1989, 1999) have employed a sickness-aversion protocol in which chicks, having pecked a neutral object (a dry colored bead) and subsequently been made sick by intraperitoneal injection of lithium chloride, will later avoid the bead. Social learning, in which one chick observes and learns from the experience of a second is another important paradigm, bypassing as it does direct physiological or pharmacological manipulation of the learner (Johnston et al. 1999a). Bradley and colleagues (1999) have explored forms of LTP in the chick forebrain that correlate with the training protocols described below. This review, however, is largely confined to the data from the passive avoidance model.

The passive avoidance task has the merits of being rapid and sharply timed (chicks peck a bead within 10 sec) and as many as 60 chicks can be trained in a single session. In the standard version of the task in our lab, day-old chicks are held in pairs in small pens, pretrained by being

THE CHICK AS A MODEL FOR MEMORY STUDIES

offered a small dry white bead, and those that peck trained with a larger (4-mm diameter) chrome or colored bead coated with the distasteful methylanthranilate (MeA) (Lossner and Rose 1983). Chicks that peck such a bead show a disgust reaction (backing away, shaking their heads, and wiping their bills) and will avoid a similar but dry bead for at least 48 hr subsequently. They continue to discriminate, however, as shown by pecking at control beads of other colours. Chicks trained on the bitter bead are matched with controls that have pecked at a water-coated or dry bead, and that peck the dry bead on test. Generally ~80% of chicks in any hatch group can be successfully trained and tested on this protocol. Each chick is usually trained and tested only once. These protocols, coupled with close observation of the chicks, enables one to distinguish the general effects of the training experience with its accompanying visual, motor, and gustatory engagements from the cellular processes involved necessarily and specifically in memory formation for the task (e.g., Rose and Harding 1984). This distinction is reflected in the data presented below. Other labs (for review, see Andrew 1991) slightly vary the protocols in ways that may affect the temporal sequence of post-training behavioral and molecular processes (Burne and Rose 1997). Nonetheless, where data are comparable, there is broad consensus concerning both the behavioral and biochemical sequelae of training among the several chick laboratories.

Both correlative and interventive strategies are possible. In the correlative approach, appropriate brain regions can be dissected from trained and control birds at specific post-training times and tissue processed for biochemical, immunocytochemical, autoradiographic, or microscopic analysis. It is also possible to prepare tissue slices (prisms) or synaptoneurosome from the chicks, enabling calcium and neurotransmitter fluxes to be determined. Braun's group (Gruss and Braun 1996; Daisley et al. 1998) has developed a microdialysis system enabling such fluxes to be measured *in vivo* during both training and testing. In the interventive approach, all the birds are trained on MeA, and injected either before or after training with drug, antibody or antisense, or vehicle, to explore the possible enhancing or amnesic effect of the agent. Chicks that peck the previously distasteful bead on test are considered to be amnesic for the training. As this pecking response requires a positive and accurate act by the bird, it also controls for effects of the agent on attentional, visual, and motor processes.

The sharply timed nature of the learning experience, together with a combination of these experimental strategies, has enabled us to identify a biochemical cascade associated with memory consolidation in the minutes to hours following training. Therefore, a change in some biochemical marker at a specific post-training time, occurring in trained chicks compared with control chicks, might imply its direct engagement in memory expression at that time. Alternatively it could indicate the mobilization of that marker as part of a sequence leading to the synthesis of a molecule, or cellular reorganization, required for expression of memory. A similar argument applies to the timing of the onset of amnesia following intracerebral drug injection.

The Temporal Cascade

2-Deoxyglucose studies revealed that two regions of the chick forebrain show enhanced metabolic activity in the 40 min following training

(Kossut and Rose 1984). These are the intermediate medial hyperstriatum ventrale (IMHV), an association “cortical” area previously implicated in visual imprinting (Horn 1985), and the lobus parolfactorius, a basal ganglia homolog (Csillag 1999). The chick brain is strongly lateralized (Andrew 1999; Rogers and Deng 1999) and many, though not all of the molecular events that we have observed are confined to the left IMHV. It is this cascade, primarily as identified by my lab, which forms the focus of the present review, although this means that it is not possible to do full justice to the work of the La Trobe group of Ng and his colleagues, which parallels my own most closely (for reviews, see Gibbs and Ng 1977; Ng and Gibbs 1991; Gibbs et al. 1991; and other references in this text). The combination of correlative and interventive methods has enabled an approximate temporal sequence to be traced. Table 1 shows the effects of injecting specific interventive agents just before or just following training and the time of onset of amnesia consequent on that injection. The cartoon of Figure 1 interprets these and the correlative and enhancement data discussed below in terms of a temporal sequence of molecular events in the IMHV following the bead peck.

Table 1: *Time of onset of amnesia for the passive avoidance task following injection of blocking agents just before or after training*

Agent ^a	Process blocked	Onset of amnesia (min)
1. Muscimol	GABA agonist	10–15
2. Nitroarginine	NO synthesis	15–30
3. TFP:W13;A3 W9;HA1004	Ca ²⁺ /CAM kinase/B50?	15–30
4. Ω-Conotoxin GVIA	N-type Ca ²⁺ channels	15–30
5. D-galactose ^b	glycosylation	30–40
6. Anti-L1 ^b	signal transduction	30–40
7. H7; HA156; H8; H9; ML9	PKA, PKC, PKG; B50 neurogranin phosphorylation	60
8. <i>c-fos</i> antisense	<i>c-fos</i> expression	60
9. α-APP antisense	β-APP expression	60
10. Anisomycin ^b	protein synthesis	60
11. NDGA	arachidonic acid synthesis	75
12. AP5, MK801	NMDA	90
13. Dantrolene	intracellular Ca ²⁺ stores	60–180
14. RU38486	glucocorticoid receptors	60–180
15. anti-BDNF	BDNF	60–180

^aReferences: (1) Clements and Bourne (1996); (2) Holscher and Rose (1993); (3) Serrano et al. (1994); (4) Clements et al. (1995); (5) Crowe et al. (1994); (6) Scholey et al. (1995); (7) Serrano et al. (1994); (8) Mileusnic et al. (1996); (9) Mileusnic et al. (1999); (10) Freeman and Rose (1995); (11) Holscher and Rose (1994); (12) Rickard et al. (1994); (13) Salinska et al. (1999); (14) Sandi and Rose (1994b); (15) Johnston et al. (1999a,b).

^bAnisomycin is also amnesic if injected 4 hr post-training; anti-L1 and 2-D-gal if injected at 5.5 hr post-training. Agents only effective during the second wave discussed in the text are not listed here.

THE CHICK AS A MODEL FOR MEMORY STUDIES

Figure 1: Pre/post synaptic parallel processing in memory formation for passive avoidance.

The First Hour

During training, and in the 5 min that follow, there is enhanced release of glutamate in the IMHV, detected both by microdialysis *in vivo* (Daisley et al. 1998), and in tissue slices (Daisley and Rose 1994). Over the same time period there is also an increase in potassium-stimulated calcium concentration in synaptoneurosomes isolated from the IMHV (Salinska et al. 1999). Within the succeeding 40 min, although we cannot assign them a precise temporal dependency, we have found increases in (1) NMDA-stimulated calcium flux in synaptoneurosomes (Salinska et al. 1999); in ligand binding to the NMDA-glutamate receptor (Stewart et al. 1992; Steele et al. 1995) and (3) phosphorylation of the presynaptic membrane protein B50 (aka GAP43) (Ali et al. 1988), coupled with a translocation of cytosolic Protein kinase C (PKC) to the membrane (Burchuladze et al. 1990). There is increased release of the putative retrograde messenger arachidonic acid, in tissue prisms prepared 30–75 min post-training, though the onset time for amnesia if the arachidonic acid synthesis is blocked with phospholipase A₂ inhibitors is delayed until 75 min (Clements and Rose 1996; Holscher and Rose 1994). Interventive studies with MK801 (Burchuladze and Rose 1992), the N-type calcium channel blocker Ω -conotoxin GVIA (Clements et al. 1995), and PKC inhibitors such as mellitin and H7 (Burchuladze et al. 1990), injected into

the IMHV either just before or just after training, all produce amnesia with an onset time of 30 min to 1 hr. GABA_A agonists are also amnesic at this time (Clements and Bourne 1996), so too is nitroarginine, which blocks synthesis of the putative retrograde messenger NO (Holscher and Rose 1993; Rickard et al. 1998). Other laboratories have found an involvement of a variety of protein kinases, notably protein kinase A (PKA), over this period (Serrano et al. 1994).

Most of these processes have been observed in other learning paradigms in mammals and are also reminiscent of the sequence identified in the induction phase of NMDA-dependent long-term potentiation (LTP) (Izquierdo and Medina 1997). An exception is our failure to observe any effect on retention of blocking postsynaptic L-type calcium channels with nimodipine. The N-type calcium channels blocked by conotoxin are generally assumed to be presynaptic in mammals, although this needs to be confirmed in the chick. The merits of the brevity of the training experience in the chick and the fairly sharply timed onset of amnesia following various pharmacological interventions, however, do make it possible to propose a more precise sequence for the various steps in the cascade than is otherwise feasible. As indicated in Figure 1, the observations also cast some light on the long-running discussion of pre-versus postsynaptic events in the initiation of LTP (Bliss and Collingridge 1993). Thus, NMDA up-regulation is temporally downstream of the initial *in vivo* increases in glutamate release and *in vitro* increases in potassium-stimulated calcium flux. These early events, together with the changes in phosphorylation of the presynaptic B50/GAP 43, and, if taken at face value, the conotoxin data, all point to presynaptic engagement. The amnesia resulting from blocking nitric oxide NO synthase with nitroarginine, which sets in by 30 min, implies two-way signaling between post- and pre-synaptic sides, and that this continued traffic is necessary if both are to undergo reconstruction during the later stages of memory formation.

It therefore would appear that the training experience generates a sequence of rapid synaptic transients that provide a temporary “hold” for the memory—the phases categorized as short and intermediate term memory by Gibbs and Ng (1977; see also Patterson et al. 1988). As well as forming the brain substrate of the remembered avoidance over this period, these transients must serve two other functions. They must initiate the sequence of pre- and post-synaptic intracellular processes that will in due course result in the lasting synaptic changes presumed to underlie long-term memory, and they must also serve to “tag” relevant active synapses, perhaps via B50 and other membrane phosphorylations so as to indicate those synapses later to be more lastingly modified.

Hours 1–8

A key step in the intracellular cascade must be the link between synapse and nucleus. Calcium is clearly a major player here, and that intracellular calcium signaling may be important is indicated by our recent observation that within 10 min post-training there is also a mobilisation of synaptoneurosomal ryanodine-sensitive calcium stores (E.J. Salinska, R.C. Bourne and S.P.R. Rose in prep.), whereas dantrolene, which blocks calcium release from these stores, injected 30 min pre- or 30 min post-training, produces amnesia by 3 hr post-training. Synaptoneurosomes are largely presynaptic, though they contain resealed postsynaptic

THE CHICK AS A MODEL FOR MEMORY STUDIES

(dendritic) elements as well, so it is not possible to distinguish whether the mobilized calcium stores are located at one, the other, or both sides of the cleft.

That activation of a number of transcription factors must be among the next steps in the process is clear from the elucidation of a role for CREB in several mammalian learning paradigms. However, we have focused on the role of immediate early genes, *c-fos* and *c-jun*. That visual stimulation alone is sufficient to activate *fos* or *jun* expression is well known, so it was not surprising that we found that passive avoidance training elicited such activation (Anokhin et al. 1991). To control for the specificity of the expression, we compared overtrained and undertrained chicks on the pebble floor task described above. Although both groups showed the pecking behavior, the learning, as opposed to the already trained group, showed a clear increase in *jun* expression (Anokhin and Rose 1991). Further evidence as to the necessity of *fos* expression for longer-term memory is provided by the observation that antisense to *c-fos*, given six or more hours pretraining, blocks its synthesis (Mileusnic et al. 1996) and chicks become amnesic within 3 hr of post-training.

One of the few universal findings in studies of biochemical processes in memory formation is that long(er)-term memory is protein synthesis-dependent (Davies and Squire 1984). Passive avoidance training is no exception, and anisomycin injected into the IMHV either before or up to some 60 min post-training results in amnesia for the avoidance. If the anisomycin is injected before training, amnesia sets in by the end of the first post-training hour, leading to the suggestion that beyond this period memory is protein synthesis-independent (Gibbs and Ng 1977). However, the earlier view that beyond this time a protein synthesis-independent, long-term memory has been established is no longer tenable. Whereas anisomycin injections 2 and 3 hr post-training are without effect on memory, injections given 4 or 5 hr post-training are amnesic in animals tested at 24 hr (Freeman and Rose 1995) as earlier found for rats by Grecksch and Matthies (1980). Therefore there is a second, downstream wave of training-related protein synthesis that we interpret as being the period during which late genes are activated and structural proteins synthesized. This is not, however, the entire explanation; other processes are also mobilized during this later time period. Whereas 30 min post-training NMDA but not AMPA receptors are engaged, 5.5 hr post-training AMPA but not NMDA receptors are upregulated, leading to an increase in AMPA-stimulated calcium flux in synaptoneurosomes. CNQX given at this time is amnesic (Steele and Stewart 1995; Salinska et al. 1999). The relationship between these events and the protein synthetic wave is still not clear.

Whereas much attention within the learning and memory community is currently directed toward the roles of the many transcription factors involved in the early phases of memory formation, we have focused on identifying the later gene products. There is considerable evidence for a role for synaptic membrane glycoproteins (Popov et al. 1981; for reviews, see Matthies 1989; Rose 1995a,b). Among the membrane glycoproteins are a variety of receptors, and the family of cell- and matrix-adherence molecules. The cell-adhesion molecules (CAMs) are transmembrane molecules, whose glycosylated extracellular domains can bind either homophilically or heterophilically, providing a mechanism for associating pre- and postsynaptic membranes. Their potential role in synaptic

plasticity has long been emphasized by Edelman (1985) (see also Pollerberg et al. 1985; Goelet et al. 1986). Neural CAM (NCAM) in particular exists in a number of isoforms. In its immature form it is relatively highly sialylated, and less adherent. The mature form is desialylated, and more adherent. This has led to the suggestion, for which there is now good empirical evidence (Doyle et al. 1992a), that synaptic restructuring, either in the context of general development, or more specifically as a result of training experiences, requires first a sialylating, deadherence step, enabling synaptic mobility to occur, and subsequently desialylation and readherence. These are not the only roles proposed for the CAMs, however; they are also likely to be involved in transmembrane signaling.

Fucose is a general glycoprotein precursor, and training chicks on MeA results in a long-lasting increased fucosylation of synaptic membrane glycoproteins. The use of the competitive inhibitor of galactose incorporation into glycoproteins, 2-deoxygalactose (2-D-gal), which prevents terminal fucosylation, was pioneered by Matthies and his colleagues. Injected into the IMHV either around the time of training, or 6–8 hr later, 2-D-gal results in amnesia in chicks tested at 24 hr (Rose and Jork 1987; Scholey et al. 1993). This suggests a double wave of glycoprotein synthesis analogous to that already found with anisomycin and comparable with that observed by the Matthies group following a brightness discrimination task in rats. These time windows are displaced with respect to the effects of anisomycin, occurring before the anisomycin-induced amnesia at the first time point, and after it at the second (Freeman and Rose 1995; Crowe et al. 1994). We interpret this as indicating that during the first period 2-D-gal is blocking post-translational glycosylation of already synthesized proteins, whereas at the second time period it affects *de novo* glycoprotein synthesis.

Among the glycoproteins whose synthesis is blocked by 2-D-gal are a number of CAMs. Two in particular are required for longer-term memory—NCAM and neuron/glia CAM (NgCAM) (aka L1) (Scholey et al. 1993, 1995). Both have also been shown to be required for maintenance of LTP (Luthi et al. 1994). NCAM levels also increase after visual imprinting (Solomon et al. 1995). Training chicks on MeA results in a redistribution of NCAM within the synaptic junction, as detected by immunogold labeling (Skibo et al. 1993; Rusakov et al. 1994). Specific blocking of NCAM synthesis with antisense, injected over the 24 hr post-hatch period before the birds are trained, does not prevent the chicks learning the avoidance, but amnesia sets in within 3 hr (Mileusnic et al. 1999). Interference with the functioning of already synthesized CAM molecules, however, is also amnesic. Therefore, if antibodies that bind to the extracellular domains of either NCAM or L1 are injected into the IMHV at 5–6 hr post-training, chicks show amnesia when tested at 24 hr (Scholey et al. 1993; 1995), a time at which the antibodies themselves are no longer detectable in the brain. Antibodies to NCAM are not amnesic if injected at other times, but antibodies to L1, injected 30 min pre-training, are also amnesic when the chicks are tested at 24 hr. The extracellular domains of L1 include fibronectin and immunoglobulin regions, and using recombinant fragments to these regions, we found that blocking the immunoglobulin domain at –30 min, but not at +5.5 hr, resulted in amnesia, whereas by contrast, blocking the fibronectin domain at +5.5 hr, but not at –30 min, was amnesic (Scholey et al. 1995). This biochemical

version of a double dissociation experiment led us to postulate that it was the cell signaling function of L1, mediated via the immunoglobulin domain, which was engaged in the early phases of memory formation, whereas the fibronectin domains of NCAM and L1 were required in the deadherence/readherence processes at the later time point. It is presumably at this time, 5–8 hr downstream of the training event, while their epitopes on the external domains are open to attack, that antibody binding can occur and therefore amnesia result.

Somewhat to our surprise, we have recently found that antibodies to two other transmembrane proteins also produce amnesia if injected 30 min pre-training, but not at later times. These are the lipid trafficking protein apolipoprotein E (ApoE), and the cell-matrix adherent amyloid precursor protein, (APP) (Lancashire et al. 1998; R. Mileusnic, C. Lancashire, A.N.B. Johnston, and S.P.R. Rose unpubl.). These effects may not be mutually independent, as there is evidence for interaction between APP and ApoE (Huber et al. 1993; Lancashire et al. 1998) and both may be involved in the transmembrane signaling processes that we have argued are required in the early stages of memory formation. As both proteins are implicated in Alzheimer's disease, further elucidation of their mode of action in normal memory formation may provide clues as to the memory impairment characteristic of that condition.

Structural Consequences

The longer-term consequence of this cascade is therefore the modification of synaptic connectivity, detectable biochemically in terms of changes in the configuration and distribution of NCAM, among other synaptic markers. The presumed end point for memory storage is modulation of synaptic connectivity, by altering synaptic number, and/or relocating or structurally modifying existing synapses and dendritic spines. Such changes have been observed in a variety of paradigms, from enriched and impoverished environments to LTP and memory formation (Chang and Greenough 1984; Bailey and Kandel 1993). Might the biochemical changes that we have observed in the chick IMHV following passive avoidance training also result in changes in synaptic morphology detected by quantitative microscopy? In a series of studies, Stewart and his colleagues (Rose and Stewart 1999) have been able to show changes in both pre- and postsynaptic elements. Thus, 24 hr post-training there is increased dendritic spine density in projection neurons of the IMHV (Patel et al. 1988), and at the same time changes in the numbers and dimensions of synaptic junctions, presynaptic boutons and synaptic vesicle number in both IMHV and lobus parolfactorius. These findings must, however, be contrasted with the observation by Wallahusen and Scheich (1987) that 7 days following acoustic imprinting, there is a sharp decrease in spine number in the relevant forebrain region (Wallhauser and Scheich 1987). These results might be reconciled if we envisage that after training there is an initial efflorescence of spines, followed by a subsequent pruning, as argued, for instance, by Edelman (1985) (see also Purves 1988). The increases in synapse number at 24 hr found by Rose and Stewart (1999) are protein-synthesis dependent. There are also transient changes in number detectable with 1 hr post-training in the right IMHV, however, which may be attributable to synapse splitting rather than de novo synapse production (for reviews of these morphological changes, see Stewart and Rusakov 1995; Rose and Stewart 1999).

Factors Affecting the Salience of Memory

Having pecked a bead coated in MeA, chicks avoid a similar but dry bead for at least 24 hr subsequently. If the aversant is made less strong, however, by, for instance, using a 10% solution of MeA in alcohol, the birds peck and display a disgust reaction but will avoid similar beads for only 6–9 hr subsequently (Sandi and Rose 1994a; see also Burne and Rose 1997). Although insofar as we have compared them, weak training initiates a similar set of synaptic transients to those produced in the strong version of the task, these are apparently not sufficient to result in gene expression, as glycoprotein synthesis does not occur. Our assumption is that the temporal relationship between the fading of the memory trace for the weak training beyond 6 hr and the wave of glycoprotein synthesis that occurs at this time with strong training is not fortuitous (Rose 1995b). A variety of factors can affect the salience of this “weak learning” experience, however, which result in memory being retained as for the strong learning.

Chicks are normally held in their pens in pairs, as this diminishes stress. If they are trained on 10% MeA and then separated, stress levels increase and retention persists for 24 hr (Johnston and Rose 1998). The normal training procedure is stressful, as is shown by the fact that 5–10 min following training, in chicks on the strong but not the weak version of the task, there is an increase in plasma corticosterone levels (Sandi and Rose 1997a). Furthermore, if corticosterone is injected into the IMHV just before or just after weak training, retention is also enhanced (Sandi and Rose 1994a). The enhancing effects of stress can be blocked by injection of antagonists of glucocorticoid receptors into the IMHV, which is rich in such receptors. Blockade of these receptors is also amnesic for strong training (Sandi and Rose 1994b), as is inhibition of peripheral corticosterone synthesis with metyrapone or aminoglutethimide (Loscertales et al. 1997). Corticosterone has effects both at the membrane and genomically, and it is relevant that we have shown that independently of training, injections of corticosterone into the IMHV will enhance glycoprotein synthesis 6 hr subsequently (Sandi et al. 1995; Sandi and Rose 1997b). As might be anticipated, the effects of corticosterone are dose-dependent in the classic inverted-U form. One microgram injected before weak training enhances retention, whereas higher doses do not; 1–5 μ g injected before strong training diminishes retention (Sandi and Rose 1997a).

Neurotrophins also affect the salience of weak training. Recombinant brain-derived neurotrophic factor (BDNF), but not NGF or NT-3, injected just before or just after weak training, will enhance 24-hr retention. Reciprocally, antibodies to BDNF are amnesic for strong training, amnesia setting in within 3 hr (Johnston et al. 1999b). How BDNF may exert its effect is not clear. There are suggestions that it may act as a retrograde messenger, that it generates an intracellular signaling cascade via TrkB receptors, and that, like corticosterone, it may interact with GABAergic systems (for review, see McKay et al. 1999). In this respect, the fact that just as GABA agonists are amnesic for strong training, antagonists enhance weak training (Clements and Bourne 1996), may be significant.

These findings are of both theoretical and practical relevance. First, they remind us that although—especially under the influence of the neurophysiological observations of synaptic interactions during LTP—cellular theories of memory formation are heavily based on Hebbian

THE CHICK AS A MODEL FOR MEMORY STUDIES

models, memory is not just a pre-/postsynaptic event. Rather, whether any particular experience is learned or not depends on a much wider array of neural and peripheral factors, humoral, and perhaps also immunological (see McGaugh 1989; Damasio 1994). The entire animal is therefore involved in any learning experience. Second, together with the observations on ApoE and APP described in the previous section, they may point the way toward developing effective agents for therapeutic intervention in conditions of memory deficit.

Memory Beyond the IMHV

This review has focused on the sequence of biochemical events occurring in the chick IMHV consequent to passive avoidance training, and I have argued that the cascade we have identified, leading as it does to measurable morphological changes in synaptic connectivity, is a necessary part of memory consolidation. Does this, however, mean that the IMHV contains some lasting representation of the association between bead and bitter taste, the elusive engram? A combination of electrophysiological and lesioning experiments that have been conducted in parallel with those described here, but are outside the remit of this review, makes clear that this is not simply the case (for review, see Rose 2000). Within the hours following training, biochemical changes occur in other brain regions than the left IMHV, including the right IMHV and lobus parolfactorius, and the memory trace, if it is such, becomes both fragmented and redistributed. The IMHV seems to retain some aspects of the memory, including color discrimination, whereas others, related perhaps to the size and shape of the bead, may be located to the lobus parolfactorius (Patterson and Rose 1992; Barber et al. 1999). Again, this points to the conclusion that learning and memory formation and retention engage not simply a discrete neuronal ensemble in a small brain region, but a much wider set of spatially and temporally dynamic processes, linked and given coherence by some form of binding mechanism (Freeman 1999; Singer 2000).

Memory Beyond the Chick

I have argued that the chick may be at least one of God's organisms for the study of the molecular processes of memory formation, but it is important to address the question of whether the processes we have observed are a special case, confined to either early learning, or to avian species. Although there are undoubtedly features that are specific to both, I would argue that our findings are of more general significance. The striking temporal parallels between the biochemical cascades found in the hippocampus following inhibitory avoidance training in rats, and in LTP, with those described here have been reviewed by Izquierdo and Medina (1997). The two "waves" of glycoprotein synthesis following training have been found in a variety of adult mammalian species and tasks, including appetitive and inhibitory avoidance and motor learning in mice and rats (Grecksch and Matthies 1980; Doyle et al. 1992b). The antibodies originally prepared against chick glycoprotein species, notably NCAM, which are amnesic when injected 5.5 hr post-training in our task, are also amnesic when injected at the same time in rats (Alexinsky et al. 1997; Rouillet et al. 1997; see also, Doyle et al. 1992b). In these cases, however, amnesia does not set in until 48 hr later, implying some more complex phase shifts in longer-term memory. One of the clear implications of the cascade we have found in the chick is that the earlier heuristic model in

which memory formation proceeds serially through a series of sequential short, intermediate, and then finally robust long-term memory, presumably in the same small ensemble of neurons, is no longer sustainable, either for the chick or for other species (DeZazzo and Tully 1995). Furthermore, the magnitude and diverse locations in space and time of the changes that we have found following training on such a simple learning task demands that we reconceptualize our model of memory storage, moving from a fixed and linear view of memory formation to a more dynamic concept, involving large ensembles of cells differentially distributed in space and time (Rose 2000).

It is clear from the diversity of receptor-mediated events that can trigger LTP (e.g., NMDA and non-NMDA dependence) that we may expect to find that the processes that initiate synaptic transients are likely to be task- and even species-dependent. The intracellular and molecular housekeeping cascades that follow from these transients, however, may well prove to be more universal, and the final involvement of CAMs in synaptic remodeling a general feature of many forms of memory. In elucidating these molecular mechanisms, and in its potential as a model system for the study of therapeutic approaches to memory impairment, the chick has earned its proper place among God's organisms.

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