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Passive Avoidance Learning in the Day-Old Chick is Modulated by GABAergic Agents

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CLEMENTS, M. P. AND R. C. BOURNE. *Passive avoidance learning in the day-old chick is modulated by GABAergic agents.* PHARMACOL BIOCHEM BEHAV 53(3) 629–634, 1996. – Injection of drugs directly into the intermediate medial hyperstriatum ventrale (IMHV) of day-old chicks, prior to training on a chrome bead dipped in either the strong aversant methyl anthranilate (MeA), or the weak aversant quinine, allows investigation of the effects of potential amnestic and memory-enhancing agents on retention of a passive avoidance task. Chicks were injected into the left and right IMHV, with either saline or muscimol (GABA agonist), 30 minutes before training on an MeA-coated bead. On test, either 10 min, 30 min or 24 h after training, birds were presented with a dry chrome bead. Normally, trained birds will avoid the test bead; however, significantly more muscimol-injected birds pecked the dry bead than did saline-injected chicks, indicating amnesia in the muscimol-injected birds. In chicks injected bilaterally into the IMHV with bicuculline, a $GABA_A$ antagonist, 30 minutes prior to training on a quinine-coated bead, avoidance scores were significantly improved on testing at 24 h compared with saline-injected control chicks, indicating enhanced retention in bicuculline-treated birds. These results suggest a role for the GABAergic system in the acquisition and retention of passive avoidance learning in the day-old chick.

GABA Muscimol Bicuculline Weak learning Strong learning

γ-AMINOBUTYRIC ACID (GABA) is the dominant inhibitory neurotransmitter in the mammalian brain, and it is well established that in rats (11,63) and mice (5,6,7,8,12,35) injections of GABAergic antagonists can enhance retention for a number of different aversively motivated tasks. Evidence suggests that delivery of the drug around the time of the training experience is most effective, and that the antagonistic action is a centrally mediated effect, because peripheral injections of bicuculline methiodide, a GABA antagonist that does not cross the blood–brain barrier, does not affect retention (7). In contrast, injections of the GABA receptor agonist, muscimol, impair retention (21,39) and block GABA antagonist-enhancement of memory (13,60,64). Benzodiazepines, which enhance the response of neuronal cells to GABA (30), cause retrograde amnesia in humans (40) and amnesia in a number of animal models employing different tasks (9,38, 55,61). Inverse agonists of the benzodiazepine receptor enhanced acquisition in mice in an habituation model of learning (62), in rats (22) and mice (62) in a passive avoidance task and, importantly, in chicks during imprinting (62).

Although much is known about the function of GABA in the mammalian central nervous system, little comparable work has been carried out in the avian brain. A number of autoradiographic (43,48,57,58) and biochemical (57) studies have indicated the presence of GABA receptors in the chick brain, with particularly high receptor density in the hyperstriatum ventrale and lobus parolfactorius (LPO; 57). These two regions of the chick forebrain, the intermediate medial hyperstriatum ventrale (IMHV) and the LPO, have also been identified in a number of studies to be sites of the formation of memory for a one-trial passive avoidance task in the day-old chick (26,45,46,52). This task employs the natural ability of young chicks to peck spontaneously at bright objects and to be able to discriminate between aversive and nonaversive substances. Thus, if a day-old chick is presented with a chrome bead coated with the bitter-tasting substance methyl anthranilate (MeA), the chick will peck once, show a strong disgust response and, subsequently, avoid a similar, but dry, bead for at least 48 h (14,26,41). Formation of long-term memory for this task involves a series of well-documented, time-related electrophysiological (42), morphological (56), and biochemical events (49,50,51). Initially these are localised, in the left

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IMHV (52) followed by rapid redistribution to other regions (i.e., the right IMHV and the LPO) (46), and ultimately result in de novo synthesis of proteins and restructuring of synaptic terminals (49). Although much of the biochemical cascade has previously been elucidated, what initiates it is still unclear. It has been suggested that this early stage may be associated with a phase of neuronal hyperpolarization and an alteration in K^+ conductance, because an intracranial injection of potassium chloride (1-2 mM) causes amnesia for the task (44). Given that the activation of the bicuculline-sensitive $GABA_A$ receptor increases postsynaptic permeability to chloride ions (25) and that GABA antagonists enhance retention of memory (5,6,11,12,13,35,64), this early phase of memory formation in the chick may be controlled locally by $GABA_A$ receptor function.

To investigate the role of the GABAergic system in acquisition and retention of passive avoidance learning in the chick we have used 2 forms of the learning task, "strong" and "weak," which allows the investigation of potential amnestic and retention-enhancing drugs, respectively. In the strong learning task, chicks are trained using a chrome bead dipped in 100% MeA. In the "weak" version of the learning task, chicks are trained on a chrome bead dipped in a weak aversant (e.g., quinine (4) or 10% MeA) (29,49,54). Chicks demonstrate a similar disgust response as they do to the strong aversant, but the avoidance response is only retained for 6-8 hours. Retention can be enhanced, however, and can persist for at least 24 h, by injecting a retention-enhancing agent (e.g., phorbol ester (29) or corticosterone) (54). Here, we report on the effect of pretraining injections of muscimol, a GABA agonist, on retention of the "strong" learning task, and pretraining injections of bicuculline, a $GABA_A$ antagonist, on retention of the "weak" learning task, in day-old chicks.

METHODS

Passive Avoidance Training

Day-old Ross 1 chunky chicks of both sexes were used in all experiments, which were carried out within the guidelines of the UK Animals Scientific Procedures Act 1986. The chicks were hatched on site and held in a communal incubator on a 12-h light/dark cycle at 38-40°C until they were 24 ± 8 h old. Animals were placed in pairs in pens illuminated by a 25 W red light and allowed to acclimatise for 1 h before subsequent training procedures. To ensure pecking behaviour was normal, birds were presented 3 times at 5-min intervals with a small (2.5 mm diameter) white bead. Only birds that pecked the pretraining bead at least 2 out of the 3 trials (more than 85%) were carried forward into the training trials. Training occurred 30 min after pretraining.

For investigations into possible amnestic effect of drugs, birds were trained by a single presentation for 30 s of a chrome bead dipped in the strong aversant MeA. These birds were then tested for their response to a similar, but dry, chrome bead either 10 min, 30 min, or 24 h after training. To investigate the possible memory-enhancing effect of drugs, birds were trained by a single presentation for 30 s of a chrome bead dipped in the weak aversant quinine (a saturated solution prepared in 20% ethanol) (4). These chicks were then tested by the single presentation of a dry chrome bead either 4 or 24 h after training. On testing, the response of the birds to the dry chrome bead was observed. Generally birds either actively avoided the bead or pecked it (those birds which showed no active response were discarded from the experiment), and an avoidance score was calculated as the percentage of all trained birds avoiding the bead on testing. An MeA or quinine-trained bird that pecked within 20 s of presentation of the dry chrome bead was regarded as amnesic for the task. Each bird was trained and tested only once. After each test, birds were presented with a white bead similar to that used for pretraining, to test the birds' ability to discriminate between an aversive (chrome bead) and a nonaversive (white bead) stimulus.

Drugs and Injection Procedure

Drugs were injected bilaterally into the left and right IMHV either 30 min before or 4 h after training. Five μl of drug or saline (0.9% NaCl) were injected directly into the IMHV using a Hamilton syringe fitted with a sleeve to control the depth of injection to 4 mm below the skull, and a specially designed head-holder (19,34,45,53). Five microlitre injections take only a few seconds, do not require the use of anesthetic, and appear to produce no adverse affects (19,34). Drugs used were muscimol (0.01 mM, 0.05 mM, and 0.1 mM prepared in saline (Sigma, Poole, U.K.) and bicuculline (0.01 mM, 0.05 mM and 0.1 mM prepared in saline (Sigma, U.K). Injections more concentrated than 0.1 mM produced behavioural abnormalities in the chicks.

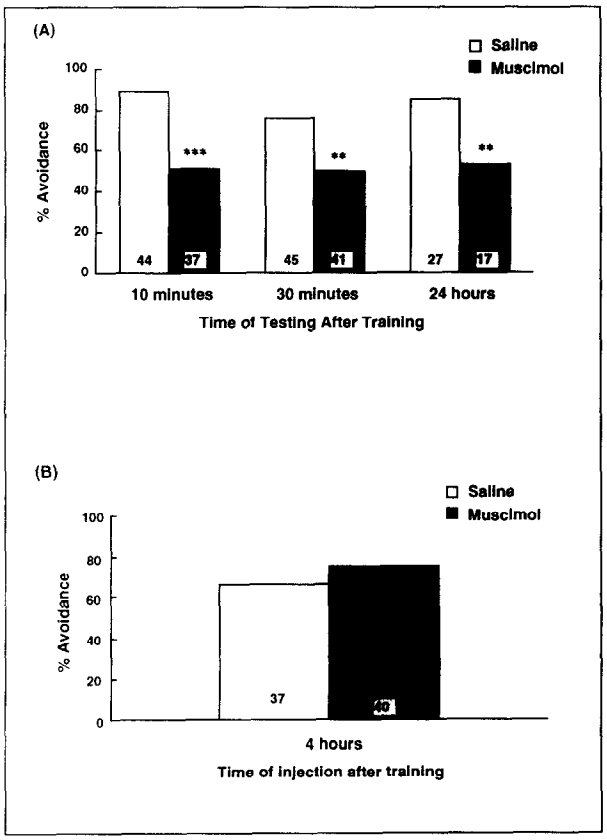

FIG. 1. Effect of muscimol and saline injections on the retention of the strong version of the passive avoidance task. (A) Muscimol (5 μl of 0.1 mM; filled histograms) injected 30 min prior to training on an MeA-coated bead produced amnesia in chicks when tested 10 min, 30 min, and 24 h after training, compared to saline-injected controls (clear histograms). (B) Muscimol injections 4 h after training on an MeA-coated bead produced avoidance scores similar to those of saline-injected controls on testing at 24 h. $^{***}p < 0.005$; $^{**}p < 0.025$ χ^2 test; number indicates number of chicks in each group.

RESULTS

The first set of experiments were designed to investigate the effect of stimulation of the inhibitory GABAergic system by muscimol on the ability of chicks to learn the passive avoidance task with the strong aversant. Muscimol, injected bilaterally into the left and right IMHV (5 μl/hemisphere, 0.1 mM) 30 min prior to training on an MeA-coated bead, produced amnesia in chicks when tested 10 min, 30 min, or 24 h after training, compared to saline-injected control chicks (Fig. 1A). Amnesia was indicated by an increase in the number of chicks pecking the dry chrome bead on testing (i.e., a reduced avoidance score). Thus, 10 min after training, 51.0% of muscimol-injected birds avoided the dry chrome bead on test compared to 88.6% avoidance in saline-injected birds ($\chi^2 = 13.74$, $df = 1$, $p < 0.005$). Thirty minutes after training, avoidance scores for muscimol- and saline-injected chicks were 52.3% and 75.5%, respectively ($\chi^2 = 5.23$, $df = 1$, $p < 0.025$), and 24 h after training avoidance scores were 53.0% and 85.0% for muscimol- and saline-injected chicks, respectively ($\chi^2 = 5.48$, $df = 1, p < 0.025$).

In contrast, bilateral injections of muscimol 4 h after training on an MeA-coated bead produced avoidance scores for chicks, when tested 24 h after training, that were not significantly different from those of saline-injected birds (Fig. 1B). Thus, 75.0% of muscimol-injected birds and 65.8% of saline-injected birds avoided the chrome bead on testing.

A dose-response curve for muscimol indicated that a 30-min pretraining injection of 0.1 mM muscimol caused amnesia when tested 30 min after training, but that neither 0.01 mM, nor 0.05 mM muscimol produced avoidance scores that were significantly different from those of saline-injected control birds (Fig. 2).

The second set of experiments was designed to test the hypothesis that inhibition of the GABAergic system using the antagonist bicuculline would enhance retention in chicks trained on the weak version of the learning paradigm. Injections of bicuculline (0.10 mM) 30 min before training on the weak aversant, quinine, produced a significant improvement in avoidance scores compared with saline-injected birds, when tested 24 h after training (Fig. 3A). Fifty percent of bicuculline-injected birds avoided the chrome bead on testing compared with 25.6% of saline-injected birds ($\chi^2 = 5.079$, $df = 1$, $p < 0.025$). However, in birds that were tested 4 h after training, following a 30-min pretraining injection of bicuculline or saline, that is, prior to the drop in retention in saline- or noninjected birds, there was no significant difference in the avoidance scores of drug- and saline-injected birds (62.2% and 59.5% avoidance in bicuculline- and saline-injected birds, respectively; Fig. 3A). In birds injected bilaterally with bicuculline 4 h after training on a quinine-coated bead, avoidance scores on testing at 24 h were not significantly different from those of saline-injected birds (39.0% and 31.0%, respectively; Fig. 3B).

A dose-response curve for bicuculline indicated that a 30-min pretraining injection of either 0.05 mM or 0.1 mM bicuculline, but not 0.01 mM, enhanced retention for the weak version of the passive avoidance task, when tested 24 h after training, compared with saline-injected controls (Fig. 4).

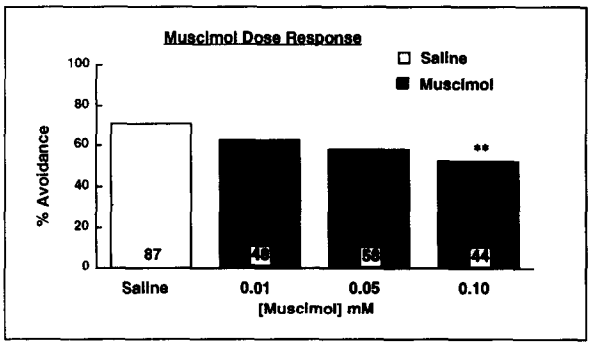

FIG. 2. Muscimol dose-response curve. A 30-min pretraining injection of 0.1 mM muscimol, but not 0.01 mM or 0.05 mM muscimol (filled histograms), produced amnesia when tested 30 min after training compared with saline-injected chicks (clear histograms). $^{**}p < 0.025$ χ^2 test; number indicates number of chicks in each group.

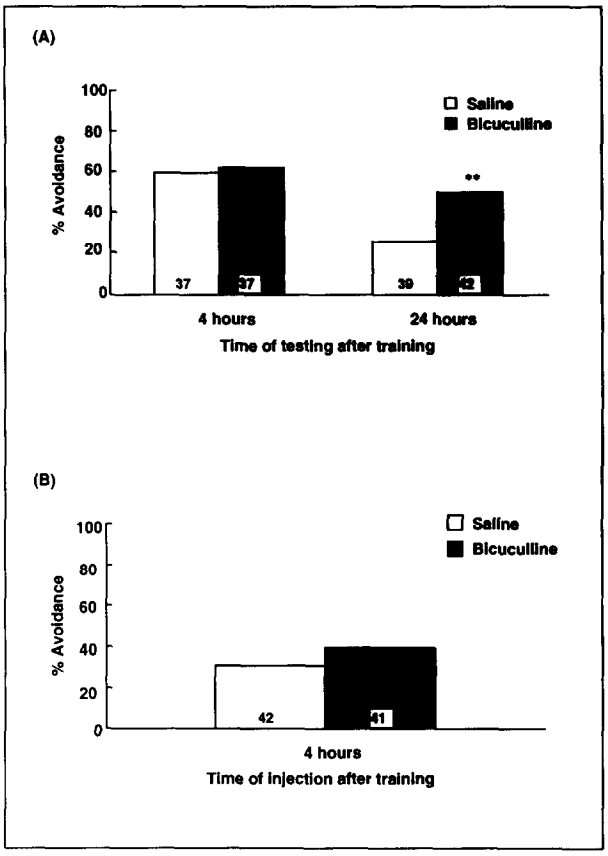

FIG. 3. Effect of bicuculline and saline injections on the retention of the weak version of the passive avoidance task. (A) Bicuculline (5 μl of 0.1 mM; filled histograms) injected 30 min prior to training on a quinine-coated bead enhanced retention for the task compared to saline-injected controls (clear histograms) when tested 24 h after training, but not 4 h after training. (B) Bicuculline injections 4 h after training on a quinine-coated bead produced avoidance scores similar to those of saline-injected controls on testing at 24 h. $^{**}p < 0.025$ χ^2 test; number indicates number of chicks in each group.

DISCUSSION

The results described here indicate that acquisition and/or the retention of memory for a simple passive avoidance learning task in the day-old chick can be modulated by alteration of the functioning of the GABAergic system. The GABA ago-

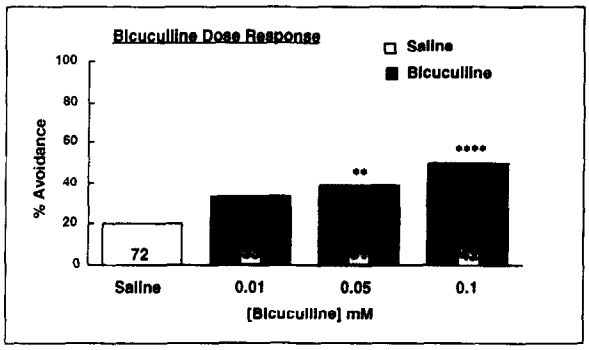

FIG. 4. Bicuculline dose-response curve. Injection of 0.1 mM or 0.05 mM bicuculline, but not 0.01 mM bicuculline (filled histograms) 30 min prior to training on a quinine-coated bead enhanced retention for the task compared to saline-injected controls (clear histograms) when tested 24 h after training. $^{**}p < 0.025$; $^{****}p < 0.005$ χ^2 test; number indicates number of chicks in each group.

nist, muscimol, when injected 30 min before training, produced amnesia, the onset of which was as early as 10 min after training, indicating an involvement of GABA at, or around, the time of training. Furthermore, injection of the $GABA_A$ antagonist, bicuculline, 30 min before training on a weak version of the avoidance task, enhanced retention for this version of the task when tested at 24 h. Neither of the drugs produced any effect on the ability of chicks to discriminate between an aversive (chrome bead) and nonaversive (white bead) stimulus, indicating a lack of effect on normal neuronal functioning (results not shown).

These results are in accordance with previous investigations on the role of the GABAergic system in retention of memory. It has been shown that bilateral infusion of muscimol into the amygdala of rats immediately after inhibitory avoidance training causes retrograde amnesia (8,37). Moreover, posttraining bilateral infusion of muscimol into the hippocampus of rats causes amnesia for inhibitory avoidance and for habituation to a novel environment (37). A number of reports have provided evidence of the enhancing effects of the $GABA_A$ antagonist bicuculline on memory retention (5,6,7,13,35), which has been associated with an interaction of the β-noradrenergic system (35). In the chick, agonists of the β-noradrenergic system enhance retention for the weak learning paradigm and appear to extend the period between intermediate and long-term memory (16,17), and it is feasible that the GABAergic and β-noradrenergic system are functioning in conjunction in the chick as they do in the rat and mouse. There is also a strong body of evidence describing the interactions of the GABAergic and cholinergic systems and their involvement in memory storage (20). Retention in rats and mice is enhanced by posttraining injections of cholinesterase inhibitors (36) or muscarinic cholinergic agonists (3,15,23,36). In the chick, pretraining injections of the cholinergic receptor antagonist, scopolamine, and the specific M_1 receptor antagonist, piperazine, cause amnesia for the one-trial passive avoidance task with an onset time of between 15 and 30 min posttraining (47). The results of the present study indicate a role for the GABAergic system in the acquisition and/or retention of the passive avoidance task in chicks, which may be as a result of a direct or indirect interaction with the cholinergic system, the noradrenergic system, both systems or, indeed, neither system. Further experiments are necessary to elucidate these potential interactions.

Prior to the experiments reported here, few potential amnestic agents have been shown to produce such early onset of amnesia for the passive avoidance task, as do the pretraining injections of muscimol. Ng and Gibbs (44) have demonstrated that intracranial posttraining injections of 1–2 mM KCl and lanthanum chloride up to 2.5 min after training, produce amnesia 5 min posttraining. These workers suggest that this stage of memory, termed short-term memory (27,28), may be associated with a phase of neuronal hyperpolarization. In the light of the findings presented here, it is reasonable to conclude that formation of this early stage of memory is controlled by a subtle modification of the state of neuronal depolarization in the IMHV. Stimulation of the GABAergic system by muscimol, leading to synaptic inhibition, blocks retention, and the specific $GABA_A$ antagonist enhances retention. We propose, therefore, that $GABA_A$ receptor activation is critical to the establishment of memory for this task and that increased synaptic inhibition prevents memory formation. Because consolidation of memory for this passive avoidance task involves a cascade of time-dependent biochemical (49,50,51) and morphological changes (56) in the chick forebrain, we suggest that a decrease in $GABA_A$-modulated synaptic inhibition may be the trigger or one part of this cascade. It is interesting to note that the induction of long-term potentiation (LTP), a neural model of memory formation, was facilitated in slices by perfusion with picrotoxin, a $GABA_A$ antagonist (31). Reduction of postsynaptic inhibition at the time of induction of LTP increased the stability of the lasting potentiation. In the chick IMHV, reduction of postsynaptic inhibition at the time of training may have the same effect on memory consolidation, enabling the transition from short to longer term memory.

The cascade of events that lead to long-term memory formation in the chick can be broadly divided into 2 phases, early events (within 30 min of the training experience) and longer-term biochemical and structural changes. The early events, which occur primarily in the IMHV, include upregulation of NMDA receptors (59), phosphorylation of presynaptic proteins (e.g., B50) (10), enhanced glutamate release (18), and release of the putative retrograde messenger nitric oxide (33). These events are paralleled by induction of mRNA for the immediate early genes c-fos and c-jun (1,2) and precede a period of protein synthesis (24) that is susceptible to inhibition by the protein synthesis inhibitor anisomycin. Although these early synaptic events are critical for acquisition of the task, formation of long-term memory for the task requires a second wave of glycoprotein synthesis some 5–8 h after training (49,50,51). It is this second wave of protein synthesis that is not apparent in chicks trained on the weak version of the training paradigm (4). Because pretraining injections of bicuculline enhance retention for the weak learning task, activation of $GABA_A$ receptors around the time of training is necessary for the consolidation of memory into a long-term event.

To clarify the role of the GABAergic system in the transition from short- to long-term memory, we investigated the requirements of the GABAergic system to initiate the second wave of protein synthesis. To test this, we injected the GABAergic agonist and antagonist 4 h after training on the strong or weak paradigm, respectively. This time point was chosen to ensure that activation or inhibition of GABA receptors preceded the onset of the second wave of protein synthesis. It has been shown that a single injection of muscimol produces a sustained increase in GABA receptor activation for

up to 2 h (32). An injection into the IMHV 4 h after training will, therefore, precede the onset of the second wave of protein synthesis and influence GABAergic activity during the early stages of the second wave. On testing at 24 h, following a 4-h posttraining injection, neither muscimol nor bicuculline produced any significant change in avoidance scores compared with saline-injected control birds. Thus, although $GABA_A$ receptor activity is involved in the modulation of memory formation, it is not required immediately prior to the second wave of protein synthesis. These results support the hypothesis that modulation of GABAergic inhibition at the time of training is critical for the development of short-term memory. Given the early onset of amnesia induced by a pretraining injection of muscimol, we suggest that memory formation for a passive avoidance task in the day-old chick is dependent on a reduction in postsynaptic inhibition at the time of training.

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REFERENCES

1. Anokhin, K. V.; Mileusnic, R.; Shamakina, I. Y.; Rose, S. P. R. Effects of early experience on c-fos gene expression in the chick forebrain. Brain Res. 544:101–107; 1991.
2. Anokhin, K. V.; Rose, S. P. R. Learning-induced increase of immediate early gene messenger RNA in the chick forebrain. Eur. J. Neurosci. 3:162–167; 1991.
3. Baratti, C. M.; Intrioni, I. B.; Huygens, P. Possible interaction between central cholinergic muscarinic and opioid peptidergic systems during memory consolidation in mice. Behav. Neural. Biol. 40:155–169; 1984.
4. Bourne, R. C.; Davies, D. C.; Stewart, M. G.; Csillag, A.; Cooper, C. Cerebral glycoprotein synthesis and long-term memory formation in the chick (Gallus Domesticus) following passive avoidance training depends on the nature of the aversive stimulus. Eur. J. Neurosci. 3:243–248; 1991.
5. Bovet, D.; McGaugh, J. L.; Oliverio, A. Effects of posttrial administration of drugs on avoidance learning of mice. Life Sci. 5: 1309–1315; 1966.
6. Breen, R. A.; McGaugh, J. L. Facilitation of maze learning with posttrial injections of picrotoxin. J. Comp. Physiol. Psychol. 54: 498–501; 1961.
7. Brioni, J. D.; McGaugh, J. L. Posttraining administration of GABAergic antagonists enhances retention of aversively motivated tasks. Psychopharmacology 96:505–510; 1988.
8. Brioni, J. D.; Nagahara, A.; McGaugh, J. L. Involvement of the amygdala GABAergic system in the modulation of memory storage. Brain Res. 47:105–112; 1989.
9. Broekkamp, C. L.; Le Pichon, M.; Lloyd, K. The comparative effects of benzodiazepines, progabide and PK 9084 on acquisition of passive avoidance in mice. Psychopharmacology 83:122–125; 1984.
10. Burchuladze, R.; Potter, J.; Rose, S. P. R. Memory formation in the chick depends on membrane-bound protein kinase C. Brain Res. 535:131–138; 1990.
11. Castellano, C.; Brioni, J. D.; McGaugh, J. L. GABAergic modulation of memory. In: Squire, L.; Lindenlaub, E., eds. Biology of Memory. New York: Schattauer Verlag; 1990:361–378.
12. Castellano, C.; Introini-Collison, I.; Pavone, F.; McGaugh, J. L. Effects of naloxone and naltrexone on memory consolidation in CD-1 mice: Involvement of GABAergic mechanisms. Pharmacol. Biochem. Behav. 32:563–567; 1989.
13. Castellano, C.; Pavone, F. Effects of ethanol on passive avoidance behaviour in the mouse: involvement of GABAergic mechanisms. Pharmacol. Biochem. Behav. 29:321–324; 1988.
14. Cherkin, A. Kinetics of memory consolidation. Role of amnesic treatment parameters. Proc. Natl. Acad. Sci. 63:1094–1100; 1969.
15. Cherkin, A.; Flood J. F. Behavioural pharmacology of memory. In: Woody, C. D.; Alkon, D. L.; McGaugh, J. L., eds. Cellular Mechanisms of Conditioning and Behavioural Plasticity. New York: Plenum; 1988:343–356.
16. Crowe, S. F.; Ng, K. T.; Gibbs, M. E. Memory consolidation of weak training experiences by hormonal treatments. Pharmacol. Biochem. Behav. 37:729–734; 1990.
17. Crowe, S. F.; Ng, K. T.; Gibbs, M. E. Possible noradrenergic involvement in training stimulus intensity. Pharmacol. Biochem. Behav. 39:717–722; 1991.
18. Daisley, J. N.; Rose, S. P. R. The effect of a passive avoidance task on the release of amino acids in vitro from the left intermediate medial hyperstriatum ventrale (IMHV) of the day-old chick. Biochem. Soc. Trans. 22:160S; 1994.
19. Davis, J. L.; Masouka, D. T.; Gerbrandt, L. K.; Cherkin, A. Autoradiographic distribution of L-proline in chicks after intracerebral injection. Physiol. Behav. 22:177–184; 1979.
20. Decker, M. W.; McGaugh, J. L. The role of interactions between the cholinergic system and other neuromodulatory systems in learning and memory. Synapse 7:151–168; 1991.
21. Ferreira, M. B. C.; Da Silva, R. C.; Medina, J. H.; Izquierdo, I. Late posttraining memory processing by the entorhinal cortex: Involvement of NMDA and GABAergic receptors. Pharmacol. Biochem. Behav. 41:767–771; 1992.
22. File, S. E.; Pellow, S. Low and high doses of benzodiazepine receptor inverse agonists respectively improve an impair performance in passive avoidance but do not affect habituation. Behav. Brain Res. 30:31–36; 1988
23. Flood, J. F.; Smith, G. E.; Cherkin, A. Memory retention: Potentiation of cholinergic drug combinations in mice. Neurobiol. Aging 4:37–43; 1983.
24. Freeman, F. M.; Rose, S. P. R.; Scholey, A. Two time windows of anisomycin-induced amnesia for passive avoidance training in the day-old chick. Neurobiol. Learning Memory 63: 291–295.
25. Geetha, N.; Hess, G. P. On the mechanism of the gamma-aminobutyric-acid receptor in the mammalian (mouse) cerebral cortex-chemical kinetic investigations with a 10-ms time resolution adapted to measurements of neuronal receptor function in single cells. Biochemistry 31:5488–5499; 1992.
26. Gibbs, M. E.; Ng, K. T. Psychobiology of memory: towards a model of memory formation. Biobehav. Rev. 1:113–116; 1977.
27. Gibbs, M. E.; Ng, K. T. Dual action of cycloheximide on memory formation in day-old chicks. Behav. Brain Res. 12:21–27; 1984.
28. Gibbs, M. E.; Ng, K. T. Hormonal influences on the duration of short-term amd intermediate stages of memory. Behav. Brain Res. 11:103–108; 1984.
29. Gulinello, M. The role of PKC in memory formation for a passive avoidance task in the one-day old chick. PhD thesis, The Open University, Milton Keynes, U.K.; 1994.
30. Haefely, W.; Kulcser, A.; Mohler, H.; Pieri, L.; Polc, P.; Schaffner, R. Possible involvement of GABA in the central actions of benzodiazpines. In: Costa, E.; Greengard, P., eds. Mechanism of Action of Benzodiazepines. New York: Raven Press; 1975:131–151.
31. Hanse, E.; Gustafsson, B. Postsynaptic, but not presynaptic, activity controls the early time course of long-term potentiation. J. Neurosci. 12:3226–3240; 1992.
32. Hardiman, M. J.; Ramnani, N; Yeo, C. H. Reversible inactivation of the cerebellum with muscimol prevents the acquisition and extinction of conditioned nictitating membrane responses. Brain Res. Assn. Abstr. 12:111; 1995.
33. Hölscher, C.; Rose, S. P. R. An inhibitor of nitric oxide synthesis prevents memory formation in the chick. Neurosci. Lett. 145: 165–167; 1992.

34. Howard, K. J.; Rogers, L. J.; Boura, A. L. A. Functional lateralization of the chicken forebrain revealed by use of intracranial glutamate. Brain Res. 188:369-382; 1980.
35. Introini-Collison, I. B.; Castellano, C.; McGaugh, J. L. Interaction of GABAergic and β-noradrenergic drugs in the regulation of memory storage. Behav. Neural. Biol. 61:150-155; 1994.
36. Introini-Collison, I. B.; McGaugh, J. L. Modulation of memory by posttraining epinephrine: Involvement of cholinergic mechanisms. Psychopharmacology 94:379-385; 1988.
37. Izquierdo, I.; Da Chuna, C.; Rosat, R.; Jerusalinsky, D.; Ferreira, M. B. C.; Medina, J. H. Neurotransmitter receptors involved in memory processing by the amygdala, medial septum and hippocampus of rats. Behav. Neural. Biol. 58:16-26; 1992.
38. Jensen, R. A.; Martinez, J. L.; Vasquez, B. J.; McGaugh, J. L. Benzodiazepines alter acquisition and retention of an inhibitory avoidance response in mice. Psychopharmacology 64:125-126; 1979.
39. Jerusalinsky, D.; Quillfeldt, J. A.; Walz, R.; Da Silva, R. C.; Bueno e Silva, M.; Bianchin, M.; Schmitz, P.; Zanatta, M. S.; Ruschel, A. C.; Paczko, N.; Medina, J. H.; Izquierdo, I. Effect of infusion of the $GABA_A$ receptor agonist, muscimol, on the role of the entorhinal cortex, amygdala, and hippocampus in memory processes. Behav. Neural. Biol. 61:132-138; 1994.
40. Lister, R. G. The amnesic effects of benzodiazepines in man. Neurosci. Biobehav. Rev. 9:87-94; 1985.
41. Lössner, B.; Rose, S. P. R. Passive avoidance training increases fucokinase activity in the right forebrain tissue of day old chicks. J. Neurochem. 41:1357-1363; 1983.
42. Mason, R. J.; Rose, S. P. R. Lasting changes in spontaneous multi-unit activity in the chick brain following passive avoidance training. Neurosci. 21:931-944; 1987.
43. Meza, G.; Gonzalez-Vivreros, M. A. T.; Ruiz, M. Specific [^{3}H]γ-aminobutyric acid binding to vestibular membranes of the chick inner ear. Brain Res. 337:179-183; 1985.
44. Ng, K. T.; Gibbs, M. E. Stages in memory formation: a review. In: Andrew, R. J., ed. Neural and Behavioural Plasticity: The use of the domestic chick as a model. Oxford: Oxford University Press; 1991:521-535.
45. Patterson, T. A.; Alvarado, M. C.; Warner, I. T.; Bennett, E. L.; Rosenzweig, M. R. Memory stages and brain asymmetry in chick learning. Behav. Pharmacol. 100:856-865; 1986.
46. Patterson, T. A.; Gilbert, D. B.; Rose, S. P. R. Pre and posttraining lesions of the IMHV and passive avoidance learning in the chick. Exp. Brain Res. 80:189-195; 1990.
47. Patterson, T. A.; Lipton, J. R.; Bennett, E. L.; Rosenzweig, M. R. Cholinergic receptor antagonists impair formation of intermediate-term memory in the chick. Behav. Neural. Biol. 54:63-74; 1990.
48. Ramirez, G.; Barat, A.; Gomez-Barriocanal, J.; Manrique, E.; Batuecas, A. Development of specific sites for [^{3}H]kainic acid and [^{3}H]muscimol in the chick optic tectum. Modulation by early changes in visual input. In: Mandel, P.; De Feudis, F. V., eds. CNS receptors—from Molecular Pharmacology to Behaviour. New York: Raven Press; 1983:187-198.
49. Rose, S. P. R. Glycoproteins and memory formation. Behav. Brain Res. 66:73-78: 1995.
50. Rose, S. P. R. How chicks make memories: the cellular cascade from c-fos to dendritic remodelling. Trends Neurosci. 14:390-397; 1991.
51. Rose, S. P. R. Synaptic plasticity, learning and memory. In: Baudry, M.; Thompson, R. F.; Davis, J., eds. Synaptic plasticity: molecular, cellular and functional aspects. Cambridge, MA: MIT Press; 1993:209-229.
52. Rose, S. P. R.; Csillag, A. Passive avoidance training results in lasting changes in deoxyglucose metabolism in left hemisphere regions of chick brain. Behav. Neural. Biol. 44:315-324; 1985.
53. Rose, S. P. R.; Jork, R. Long-term memory in chicks is blocked by 2-deoxygalactose, a fucose analogue. Behav. Neural. Biol. 48: 246-258; 1987.
54. Sandi, C.; Rose, S. P. R. Corticosterone enhances long-term retention in one-day-old chicks trained in a weak passive avoidance learning paradigm. Brain Res. 647:106-112; 1994.
55. Soubrié, P.; Simon, P. Comparative study of the antagonism of bemegride and picrotoxin on behavioural depressant effects of diazepam in rats and mice. Neuropharmacology 17:121-125; 1978.
56. Stewart, M. G. Morphological correlates of long term memory in the chick forebrain consequent on passive avoidance training. In: Squire, L. R.; Lindenlaub, E., eds. The biology of memory (Symposia Medica Hoechst 23) Stuttgart/New York: Schattauer FK, Verlag; 1990:193-215.
57. Stewart, M. G.; Bourne, R. C. Ontogeny of [^{3}H]muscimol binding to membranes of chick forebrain. Exp. Brain Res. 65:707-710; 1987.
58. Stewart, M. G.; Bourne, R. C.; Chmielowska, J.; Kalman, M.; Csillag, A.; Stanford, D. Quantitative autoradiographic analysis of the distribution of [^{3}H]muscimol binding to GABA receptors in chick brain. Brain Res. 456:387-391; 1988.
59. Stewart, M. G.; Bourne, R. C.; Steele, R. J. Quantitative autoradiographic demonstration of changes in binding to NMDA-sensitive [^{3}H]glutamate and [^{3}H]MK-801, but not [^{3}H]AMPA receptors in chick forebrain 30 minutes after passive avoidance training. Eur. J. Neurosci. 4:936-943; 1992.
60. Swartzwelder, H. S.; Tilson, H. A.; McLamb, R. L.; Wilson, W. A. Baclofen disrupts passive avoidance retention in rats. Psychopharmacology 92:1-7; 1987.
61. Thiébot, M.-H. Some evidence for amnesic-like effects of benzodiazepines in animals. Neurosci. Biobehav. Rev. 9:95-100; 1985.
62. Venault, P.; Chapoutier, G.; Prado de Carvalho, L.; Simiand, J.; Morre, M.; Dodd, R. H.; Rossier, J. Benzodiazepine impairs and β-carboline enhances performance in learning and memory tasks. Nature, 321:864-866.
63. Yonkov, D. I.; Georgiev, V. P. Memory effects of GABAergic antagonists in rats trained with two-way active avoidance tasks. Acta Physiol. Pharmacol. Bulg. 11:44-49; 1985.
64. Yonkov, D.; Georgiev, V.; Kambourova, T.; Opitz, M. Participation of angiotensin II in learning and memory. III. Interactions of angiotensin II with GABAergic drugs. Meths. Find. Exp. Clin. Pharmacol. 9:205-208; 1987.