The Role of Muscarinic and Nicotinic Cholinergic Neurotransmission in Aversive Conditioning: Comparing Pavlovian Fear Conditioning and Inhibitory Avoidance

Matthew R. Tinsley, Jennifer J. Quinn, and Michael S. Fanselow

Department of Psychology, University of California, Los Angeles, California 90095, USA

Aversive conditioning is an ideal model for studying cholinergic effects on the processes of learning and memory for several reasons. First, deficits produced by selective lesions of the anatomical structures shown to be critical for Pavlovian fear conditioning and inhibitory avoidance (such as the amygdala and hippocampus) resemble those deficits seen in human pathological conditions resulting in damage to these same structures. This supports the suggestion that experimental findings on learning and memory in animal models are informative about similar processes in humans. Second, because aversive conditioning is learned rapidly, even with a single conditioning trial, the temporal dynamics of the underlying processes can be examined with a very fine degree of resolution. Third, the fear memories generated by aversive conditioning procedures tend to be very stable over long time periods. For example, we have observed robust freezing to both tone and context up to 16 mo following fear conditioning (Gale et al. 2003). Finally, fear is a motivational system that has evolved to protect an animal from danger. Fear responses observed under laboratory conditions are similar to those observed in the animal’s natural habitat, meaning that the results of aversive conditioning procedures typically have external validity.

Pavlovian Fear Conditioning and Inhibitory Avoidance: Procedures and Neural Substrates

Although a variety of conditioning procedures have been used to examine cholinergic effects on aversive conditioning, the two most popular recently have been Pavlovian fear conditioning and inhibitory, or passive, avoidance. In Pavlovian fear conditioning procedures, the animal is placed in a conditioning context and a previously neutral stimulus such as a tone (the conditional stimulus, CS) is paired with an aversive stimulus such as electric shock (the unconditional stimulus, US). As a result of the pairing of tone and context with shock, both the tone and context acquire the ability to elicit a defensive behavioral response such as freezing (the conditional response, CR) during re-exposure. In a typical inhibitory avoidance procedure, the animal is placed into a chamber with two separate compartments. One compartment is brightly lit while the other is dimly lit. The animal is placed into the bright compartment, and the latency to enter the dim compartment is recorded. After the animal enters the dim compartment, the passageway is closed and the animal receives inescapable footshock. On a subsequent test day, the animal is replaced in the bright compartment, and its latency to enter the dim compartment is recorded.

It is clear that these two training procedures have much in common. In both procedures, the animal experiences a pairing of a previously neutral stimulus, context or tone, with shock. In each case, it is likely that Pavlovian conditioned associations between the context and shock influence subsequent behavior. However, there are also important differences between these two procedures. In Pavlovian fear conditioning, the presentation of shock is independent of the animal’s behavior: The contingency between the CS and US is determined by the experimenter. In inhibitory avoidance training, however, the animal must make a response, entering the dim chamber, before being shocked. As a result, it is likely that the footshock acts both to condition the dimly lit compartment as an aversive contextual CS through Pavlovian conditioning processes and to punish the behavior of entering the dim compartment through operant conditioning processes.

The underlying neural circuitry of Pavlovian fear conditioning has been examined extensively using a variety of fear responses (for review, see Fendt and Fanselow 1999) and has been demonstrated to include the amygdala, hippocampus, and frontal cortex, depending on procedure. The frontotemporal amygdala (the lateral and basolateral nuclei; Swanson and Petrovich 1998) is critical for both the acquisition and expression of conditional fear (see Maren and Fanselow 1996 for review). Pre- or posttraining lesions of the frontotemporal amygdala (FTA) eliminate conditional fear (LeDoux et al. 1988; Davis 1992; Maren et al. 1996b). FTA inactivation (Helmstetter and Bellgowan 1994; Muller et al. 1997) or blockade of N-methyl-D-aspartate (NMDA) receptor activity within the FTA (Maren et al. 1996a; Lee et al. 2001) also blocks the acquisition and expression of contextual and cued fear conditioning. This series of findings has led to the conclusion that this component of the amygdala is involved in both the neural encoding and storage of Pavlovian conditioned fear memories (Fanselow and LeDoux 1999).

showed that large pretraining lesions of the amygdala attenuate, but do not block, inhibitory avoidance learning. Additionally, postraining amygdala lesions do not block inhibitory avoidance retention (Parent et al. 1992, 1994, 1995; Parent and McGaugh 1994). Although these results contrast with those from Pavlovian fear conditioning described above, they are consistent with results from other procedures that include a component of instrumental conditioning. Schafe et al. (1998) have demonstrated that lesions of the FTA affect conditioned taste aversion learning when the taste CS is simply presented but not when CS presentation is contingent on the animal completing an instrumental response. More recently, Lehmann et al. (2003) have demonstrated that inactivation of the BLA with tetrodotoxin during shock probe training reduces subsequent avoidance of the probe. Killcross et al. (1997) have also demonstrated differential roles of amygdala nuclei in conditioned suppression and active avoidance, further indicating that the role of the amygdala may be different in instrumental and Pavlovian tasks. These findings, and the greater inherent complexity of the inhibitory avoidance task, indicate that the role of the amygdala in Pavlovian fear conditioning would be limited and inhibitory avoidance may well differ. Given the extensive literature on intra-amygdala cholinergic manipulations in inhibitory avoidance and the different effects of cholinergic manipulations in studies using inhibitory avoidance and Pavlovian fear conditioning (described below), this procedural difference should be an important caveat to any general conclusions about the role of cholinergic transmission in aversive learning and memory.

The hippocampus is necessary for contextual and trace tone fear conditioning, but not for delay tone conditioning (e.g., Kim and Fanselow 1992; Phillips and LeDoux 1992; Quinn et al. 2002). Infusions of either NMDA or acetylcholine receptor antagonist drugs into the hippocampus during training and pre-exposure to the contextual cues of the CS have been shown to impair acquisition of the task (Maren and Fanselow 1995; Fendt and Fanselow 1999). However, inactivation of the hippocampus following training produces a temporally graded retrograde amnesia for contextual fear conditioning (e.g., Kim and Fanselow 1992; Anagnostaras et al. 1999a). This pattern of results, as well as a substantial body of additional literature, has led to the suggestion that the role of the hippocampus in Pavlovian fear conditioning is to form representations of certain classes of CS rather than in the formation of the CS-US association (Maren and Fanselow 1995; Fendt and Fanselow 1999). Hipsy, inactivation of the hippocampus during training would be limited and inhibitory avoidance may well differ. Given the extensive literature on intra-amygdala cholinergic manipulations in inhibitory avoidance and the different effects of cholinergic manipulations in studies using inhibitory avoidance and Pavlovian fear conditioning (described below), this procedural difference should be an important caveat to any general conclusions about the role of cholinergic transmission in aversive learning and memory.

In conclusion, there are important similarities between Pavlovian fear conditioning and inhibitory avoidance. Both are rapidly acquired, averagely motivated forms of learning that use heavily overlapping neural substrates. In most cases, and to the extent that they have been examined, these substrates perform the same functions in each task. There are, however, important differences between these tasks that seem to be related to the additional complexity of inhibitory avoidance. For one, the role of the amygdala in inhibitory avoidance differs in a manner that is somewhat consistent with other forms of amygdala-modulated learning that include an operant requirement (Maren 2003).
Given the importance of the amygdala in cholinergic modulation of aversive learning, this distinction is likely to prove necessary for a complete understanding of the role of acetylcholine in these procedures.

**Basal Forebrain Lesions and Pavlovian Fear Conditioning**

The “basal forebrain” is the major source of cholinergic innervation to an array of forebrain structures known to be involved in aversive conditioning, including the amygdala, hippocampus, and frontal cortex. Within the basal forebrain, the predominant cell types are cholinergic and GABA-ergic neurons, with a lesser number of smaller peptidergic neurons. Within the continuum of basal forebrain regions, two areas have been investigated most extensively because of their discrete projections. The nucleus basalis magnocellularis (nBM) projects to the frontal cortex and the frontotemporal amygdala, whereas the medial septal area (MSA) projects to the hippocampus (for a review of central cholinergic fields. However, these effects are confounded with alterations in other neurotransmitter systems caused by the loss of noncholinergic cell bodies. Despite this lack of selectivity, excitotoxic lesions of the basal forebrain have demonstrated effects on Pavlovian fear conditioning. McAlonan et al. (1995) investigated the effects of AMPA-induced lesions of the septohippocampal projection on Pavlovian trace fear conditioning and found a decrease in trace tone conditioning at longer, but not shorter, trace intervals. Schauz and Koch (1999) investigated the effects of quinolinic acid lesions of the nBM, a procedure demonstrated to cause damage to the cholinergic innervation of the amygdala, on latent inhibition (LI) of fear-potentiated startle. They found no effect of lesions in their non-LI group, indicating that disruptions of cholinergic transmission in the amygdala do not affect the Pavlovian delay fear conditioning used in fear-potentiated startle.

With the advent of the selective cholinergic immunotoxin 192 IgG-saporin, lesions can be made within the basal forebrain that produce massive degeneration of cholinergic input specifically (e.g., Baxter et al. 1995). Conner et al. (2003) compared the effect of combined nBM and MSA lesions on delay tone fear conditioning and found no effect of the lesion on activity suppression caused by presentations of the CS in a novel context. Unfortunately, they did not test the effects of these lesions on contextual fear.

The effects of medial septal cholinergic cell body lesions are largely consistent with the effects of hippocampal lesions in affecting trace tone, and not delay tone, conditioning. Further studies are required to determine whether cholinergic selective lesions, like excitotoxic hippocampal lesions, affect context conditioning. Additional studies are also required to determine whether these lesions show the same temporally graded effects on consolidation as posttraining hippocampal lesions. Although the lack of an effect of quinolinic acid lesions of the nBM on the acquisition of conditional fear, as measured with fear-potentiated startle (Schauz and Koch 1999), is surprising given their effect on cholinergic afferents to the amygdala, further study with selective immunotoxin may be required to determine that cholinergic transmission in the amygdala is not involved in delay fear conditioning. In addition, it would be interesting to determine nBM cholinergic lesions disrupt trace tone conditioning, as recent evidence indicates frontal cortex involvement in this procedure.

**Basal Forebrain Lesions and Inhibitory Avoidance**

Basal forebrain lesion studies have also been performed in inhibitory avoidance studies. Power and McGaugh (2002) used the nonselective excitotoxin phthalic acid, which has been shown to reduce choline acetyltransferase activity in the amygdala more than in the cortex (Mallet et al. 1995), to unilaterally lesion the nBM-FTA cholinergic pathway prior to training. They found that phthalic acid-lesioned animals showed significantly reduced inhibitory avoidance learning. This reduction could be rescued with ipsilateral infusions of the muscarinic agonist oxotremoreline at the acetylcholinesterase inhibitor phystostigmine into the FTA. Lesioned rats also showed slowed acquisition when trained on a continuous multiple-trial version of the inhibitory avoidance task and reduced memory consolidation when tested 48 h after this training. Hence, these results indicate effects on both rate of acquisition and consolidation.

The same group has also investigated the effects of the acetylcholine-selective immunotoxin 192 IgG-saporin (see also Zhang et al. 1996). Power et al. (2002) lesioned the nBM 8 d prior to inhibitory avoidance training and compared the effects of posttraining intra-amygdala norepinephrine infusions on subsequent inhibitory avoidance performance. Unlike pretraining phthalic acid lesions, saporin lesions had no effect on inhibitory avoidance learning. They did, however, block the enhancing effect of posttraining norepinephrine infusions. This lack of an effect with 192 IgG-saporin lesions may be due to the immunotoxin’s selective effect on cortical projections and comparative lack of effect on amygdalopetal cholinergic projections (Power et al. 2003).

**Pharmacological Muscarinic Manipulations and Pavlovian Fear Conditioning**

Results from studies of pharmacological muscarinic cholinergic manipulations on Pavlovian fear conditioning show inconsistent effects, with muscarinic receptor activation being implicated in both the acquisition and consolidation of contextual, but not delay tone, fear conditioning. Pretraining injections of the muscarinic cholinergic antagonist scopolamine reduce acquisition of contextual fear conditioning in rats (Anagnostaras et al. 1995, 1999b), at a dose that did not affect simultaneously conditioned delay tone fear, in a procedure using multiple conditioning trials. Immediate and 24 h posttraining manipulations in both adult and juvenile (20–25 day old) animals in these studies have no effects, indicating cholinergic involvement in acquisition, but not consolidation (Anagnostaras et al. 1999b). In contrast, and using juvenile (23 day old) rats, Rudy (1996) found that injections of scopolamine either before or up to 3 h after Pavlovian fear conditioning disrupted both tone and context conditioning when a single training trial was given, also indicating muscarinic cholinergic effects on memory consolidation. However, when multiple training trials were given, no posttraining effect was found on tone fear.

These results indicate a crucial factor in determining how systemic muscarinic cholinergic treatment affects Pavlovian fear conditioning is the number of training trials given in a session. In those cases in which multiple trials are given, there is either no effect (Anagnostaras et al. 1995, 1999b) or a diminished effect (Rudy 1996) of posttraining muscarinic antagonism (but see Wallenstein and Vago 2001). In contrast, where a single shock presentation is used (Rudy 1996), posttraining muscarinic blockade does influence memory consolidation. This distinction may also help to explain the differences between Pavlovian conditioning results and inhibitory avoidance studies, which typically find postraining effects and generally use a single shock procedure (see below).
The effects of muscarinic antagonism on Pavlovian fear conditioning may be due to alterations in the muscarinic M1 receptor function. Fornari et al. (2000) examined the effect of a range of pretraining doses of the M1 muscarinic antagonist dicyclo- mine on the acquisition of fear conditioning and inhibitory avoidance. Consistent with previous studies using scopolamine, pretraining systemic injection with dicycloxine dose-dependently impaired contextual fear conditioning without affecting cued fear conditioning. Unfortunately, because the study did not include posttraining manipulations, it cannot be determined whether this is an effect on acquisition or consolidation of the fear memory.

The effects of central administration of muscarinic agents are also consistent with an effect on consolidation of Pavlovian contextual fear conditioning. Pretraining scopolamine infusions into the dorsal hippocampus block the acquisition of contextual fear conditioning (Gale et al. 2001; Wallenstein and Vago 2001). However, posttraining infusions have a similar effect (Wallenstein and Vago 2001), implying that this effect may be on consolidation. Posttraining intra-amygdala infusion of the muscarinic agonist oxotremorine enhances consolidation of contextual fear conditioning (Cangioli et al. 2002), whereas administration of scopolamine disrupts it (Passani et al. 2001). Posttraining intra-amygdala infusion with a histaminergic H1 agonist or antagonist, which decrease and increase cholinergic tone in the amygdala, respectively (Passani et al. 2001; Cangioli et al. 2002), have also been shown to affect long-term memory for contextual fear conditioning, potentially through the same muscarinic receptor-dependent mechanisms (Passani et al. 2001; Cangioli et al. 2002).

Comparatively little has been published on the effects of muscarinic manipulations on the retrieval of Pavlovian conditioned fear memories. Greba et al. (2000) used a fear-potentiated startle procedure to determine the effect of intraventricular temporal area (VTA) administration of a muscarinic antagonist. They found that infusions of the muscarinic antagonist methylscopolamine into the VTA disrupt fear potentiation of startle without affecting baseline startle amplitude. This may indicate that muscarinic cholinergic modulation of dopaminergic activity may be involved in mediating recall for fear memories by modulating dopamine release in the amygdala (Greba et al. 2000).

Pharmacological Muscarinic Manipulations and Inhibitory Avoidance

There has been a long history of investigating the effects of muscarinic cholinergic manipulations on learning and memory using inhibitory avoidance (e.g., Meyers 1965; for reviews, see Bammer 1982; Prado-Alcala 1995; Power et al. 2003). These studies have typically used posttraining manipulations, focusing on effects on memory consolidation and avoiding the possibility of confounding these effects with those on acquisition and expression (McGaughey 1966). It has been reported that posttraining cholinergic and muscarinic agonist injection enhances performance of inhibitory avoidance (Baratti et al. 1979) and that central muscarinic agonist treatment has the opposite effect (Izquierdo et al. 1992). Researchers have also used receptor-selective systemic treatments to further investigate the mechanisms underlying these effects. Pretreatment administration of relatively selective muscarinic M1 receptor antagonists such as pirenzepine (Caulfield et al. 1983; Worms et al. 1989) and dicycloxine (Fornari et al. 2000) impair performance of inhibitory avoidance. Posttraining systemic administration of M1 antagonists such as biperidene and trihexyphenidyl (Roldan et al. 1997) or dicycloxine (Giachetti et al. 1986) also impair performance of inhibitory avoidance, indicating that the effect of M1 antagonism may be an impairment of memory consolidation.

Central manipulations in the hippocampus, cortex, amygdala, and striatum have also demonstrated cholinergic effects on inhibitory avoidance. Hippocampal infusions of the muscarinic agonist oxotremorine or muscarinic toxins with M1-agonist-like properties in the hippocampus enhance retention of inhibitory avoidance (Izquierdo et al. 1992; Jeruzalinsky et al. 1993) that can be blocked by scopolamine (Jeruzalinsky et al. 1993). Similar effects have been found in the anterior cingulate cortex, with posttraining scopolamine infusions impairing performance of inhibitory avoidance (Riekki et al. 1995).

There is a much more extensive literature on cholinergic effects in the amygdala with posttraining intra-amygdala infusion of the muscarinic antagonist scopolamine attenuating performance of inhibitory avoidance (Izquierdo et al. 1992; for review, see Power et al. 2003) and treatment with the muscarinic agonist oxotremorine enhancing inhibitory avoidance, an effect that is blocked by coinjection of atropine (Introini-Collison et al. 1996). Studies focusing on other transmitter systems have also shown effects consistent with the primary role of amygdala muscarinic receptors in memory consolidation. Intra-amygdalar flunarizine, a calcium antagonist, and glucocorticoid enhancement of memory consolidation are all blocked by doses of atropine that have no effect on their own (Introini and Baratti 1984; Dalmaz et al. 1993; Power et al. 2000).

There is also a substantial body of research on the role of intrastriatal cholinergic manipulations affecting consolidation of inhibitory avoidance (for review, see Prado-Alcala 1995). Posttraining intra-striatal muscarinic blockade attenuates performance of inhibitory avoidance (Haycock et al. 1973), an effect that can be reduced by striatal coadministration of choline (Solana-Figueroa and Prado-Alcala 1990). These effects of intrastriatal cholinergic antagonists on memory consolidation are highly dependent on training parameters and shock intensity in particular. Using high levels of shock intensity protected inhibitory avoidance consolidation from the disruptive effects of posttraining intrastriatal atropine (Giorlando and Prado-Alcala 1986).

Pharmacological Nicotinic Manipulations and Pavlovian Fear Conditioning and Inhibitory Avoidance

There is a wealth of literature showing nicotinic effects on a variety of cognitive functions, including working memory (Poincheval-Fuhrmann and Sara 1993; Levin 2002), spatial learning (Bernal et al. 1999), and covert attention (Stewart et al. 2001). Early studies on the role of nicotinic manipulations in aversive conditioning used active avoidance (e.g., Bovet et al. 1966; Oliviero 1966) and there remain comparatively few studies that have examined effects of pharmacological nicotinic manipulations on the acquisition and consolidation of Pavlovian fear conditioning and inhibitory avoidance.

Systemic, acute pretraining injections of nicotine, the archetypal agonist at nicotinic receptors, 5 to 20 min prior to Pavlovian fear conditioning in rats, reduce levels of context fear during a subsequent test session (Szyndler et al. 2001). These effects are not caused by unconditional increases in freezing caused by the nicotine injection itself or are the result of changes in pain sensitivity. However, no posttraining injection of nicotine was given, making it impossible to determine whether this effect was on acquisition or consolidation of fear conditioning. This behavioral effect is not present in animals receiving six daily nicotine injections prior to training (Szyndler et al. 2001), indicating that they become tolerant to the effects of systemic nicotine.

Gould and Wehner (1999) also examined the effects of systemic nicotine on Pavlovian fear conditioning in mice. They found that nicotine given on acquisition and retrieval (but not...
on acquisition or retrieval alone) enhances contextual but not cued fear conditioning (Gould and Wehner 1999). Treatment with the nicotinic antagonist mecamylamine on both the training and test days blocked this nicotine effect but had no effect when administered alone. They suggested that this result may potentially be due to a state-dependency of learning effect similar to that found with nicotine in humans (Warburton et al. 1986). Gould and Higgins (2003) have subsequently found that nicotine treatment prior to training and test, but not training or test alone, enhanced conditioning, replicating the findings of Gould and Wehner (1999). Additionally, animals treated with nicotine prior to training and test showed enhanced conditioning 7 d after training during a drug-free test, indicating that this enhancement was not due to state-dependency. This effect was not seen in animals that received nicotine prior to training and received nicotine the following day but without a test of conditioned fear, indicating that the enhancement may involve retrieval processes.

Posttraining intracerebroventricular infusions of acetylcholine or nicotine have been shown to enhance inhibitory avoidance. This effect is reduced by coinfusion of histamine or mecamylamine (Eidi et al. 2003). Developmental studies have indicated a role of amygdala nicotinic receptors with pretraining nicotine infusions enhancing inhibitory avoidance when delivered on postnatal day 20. Pretraining amygdala mecamylamine infusions attenuated inhibitory avoidance conditioning from postnatal day 11, showing their strongest effects at day 16 and waning from that point forward (Błozowski and Dumery 1987). There is also evidence of nicotinic effects on memory retrieval from inhibitory avoidance studies. Systemic nicotine administration 15 min prior to a retrieval test increased inhibitory avoidance (Zarrindast et al. 1996). This effect was opposed by the centrally acting antagonist mecamylamine but not the peripherally acting antagonist hexamethonium or the muscarinic antagonist atropine.

Genetic Muscarinic Manipulations and Effects on Pavlovian Fear Conditioning

Genetic manipulations have also been used to examine the role of the muscarinic cholinergic system in Pavlovian fear conditioning, but not yet on inhibitory avoidance. Miyakawa et al. (2001) reported on an M1 receptor knockout mouse that showed reduced freezing during delay fear conditioning and a subsequent tone test, but normal levels of context fear when tested 24 h later. However, when tested 4 wk after training, the M1 knockout mice showed significantly less freezing than wild-type controls across the duration of the test.

Anagnostaras et al. (2003) investigated another strain of M1 receptor knockout mice. They found a complex pattern of effects on learning and memory without changes in overall levels of activity or shock reactivity. When mice were tested 24 h following training, the M1 knockout mice showed enhanced contextual and normal delay tone memory. However, when the animals were tested 30 d after conditioning, M1 knockout mice showed impaired contextual conditioning and normal delay tone memory. Based on these data, and data from other behavioral tasks they report in this paper, Anagnostaras et al. (2003) conclude that M1 knockout mice show a deficit in hippocampal–cortical interaction that manifests in tests of Pavlovian conditioning as impaired consolidation of contextual memory. They suggest that this deficit is not simply mnemonic but, instead, represents a general bias of hippocampal function toward acquisition of new information and away from recall of previously acquired information (Hasselmo 1999; Fransen et al. 2002).

Genetic Nicotinic Manipulations and Pavlovian Fear Conditioning and Inhibitory Avoidance

Mice with reduced function of two classes of nicotinic receptor subunits, the α7 and β2 subunits, have been assessed for changes in aversive conditioning. Mice homozygous for knockout of the α7 receptor subunit showed no differences in either context or tone fear following delay fear conditioning, compared with wild-type controls (Paylor et al. 1998). Calderone et al. (2000) determined that aged (9–20 month old) male but not female or young (2–4 month old) β2 knockout mice displayed deficits in context and tone fear following delay fear conditioning. They concluded that under normal circumstances, nicotinic receptors containing β2 subunits are not required for normal performance in Pavlovian fear conditioning.

Picciotto et al. (1995) examined the effects of β2 knockout on inhibitory avoidance and found that whereas mutant animals showed enhanced inhibitory avoidance, unlike wild-type animals they failed to show a facilitation of consolidation following posttraining nicotine injection. Recently this group has examined this effect more closely using transgenic mice with regionally and temporally restricted expression of the β2 receptor subunit (King et al. 2003). They found that mice that express the β2 receptor subunit only in cortex and thalamus show normal levels of inhibitory avoidance, and significantly less inhibitory avoidance than β2 knockout mice. Subsequently, they examined whether β2 expression in cortex and thalamus was necessary for normal acquisition of inhibitory avoidance by using a doxycycline-inducible knockout of the β2 receptor subunit gene and found that this manipulation did not affect learning and performance of inhibitory avoidance despite the absence of the β2 subunit. They concluded that the effect of β2 receptor subunit knockout on inhibitory avoidance is caused by developmental effects possibly related to the development of glutamatergic synapses.

Conclusions

Manipulations of muscarinic and nicotinic cholinergic neurotransmission have been demonstrated to affect every aspect of aversive conditioning. Pharmacological experiments have demonstrated effects on acquisition, consolidation, and retrieval of both muscarinic and nicotinic pharmacological treatments. Genetic manipulations have demonstrated developmental and systems-level effects. Lesion studies have demonstrated effects on trace tone acquisition. Unfortunately, because a comprehensive and systematic approach has rarely been taken, no unifying picture is presently available of the role of cholinergic systems in aversive conditioning. One major problem is the lack of studies that look at a range of learning and memory processes: Inhibitory avoidance procedures have proven very productive for assessing the effect of posttraining cholinergic manipulations on performance, but very few inhibitory avoidance studies have assessed effects on acquisition or retrieval. Also of concern is the lack of consistency following posttraining muscarinic antagonist treatment in Pavlovian fear conditioning studies. A systematic, parametric approach may be required to determine why these treatments block consolidation of cued and contextual fear in some procedures and not others. The complexities obtained with cholinergic manipulations are at least partly due to the fact that cholinergic neurotransmission modulates the functions of the amygdala, cortex, and hippocampus, each of which plays different roles in various forms of aversive conditioning.

The study of cholinergic involvement in learning and memory is of great importance for understanding the basic neurobiology of these processes and in developing treatments for neurodegenerative disorders, cognitive impairment and aging.
Aversive conditioning provides an efficient, tractable and well-described set of procedures for examining this involvement. Further research and the development of new neurobiological techniques will allow continued expansion of our understanding of the roles of acetylcholine transmission in learning and memory.

REFERENCES


The Role of Muscarinic and Nicotinic Cholinergic Neurotransmission in Aversive Conditioning: Comparing Pavlovian Fear Conditioning and Inhibitory Avoidance

Matthew R. Tinsley, Jennifer J. Quinn and Michael S. Fanselow

*Learn. Mem.* 2004, 11:
Access the most recent version at doi:10.1101/lm.70204

References

This article cites 99 articles, 17 of which can be accessed free at:
http://learnmem.cshlp.org/content/11/1/35.full.html#ref-list-1

License

Email Alerting Service
Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article or click here.