The Spanish Journal of Psychology
2003, Vol. 6, No. 2, 155-167

1138-7416

Neuroscience of Pavlovian Conditioning: A Brief Review

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Current knowledge on the neuronal substrates of Pavlovian conditioning in animals and man is briefly reviewed. First, work on conditioning in aplysia, that has showed amplified pre-synaptic facilitation as the basic mechanism of associative learning, is summarized. Then, two exemplars of associative learning in vertebrates, fear conditioning in rodents and eyelid conditioning in rabbits, are described and research into its neuronal substrates discussed. Research showing the role of the amygdala in fear conditioning and of the cerebellum in eyelid conditioning is reviewed, both at the circuit and cellular plasticity levels. Special attention is given to the parallelism suggested by this research between the neuronal mechanisms of conditioning and the principles of formal learning theory. Finally, recent evidence showing a similar role of the amygdala and of the cerebellum in human Pavlovian conditioning is discussed.
Keywords: Pavlovian conditioning, neural mechanisms, learning theories

El artículo revisa brevemente los conocimientos actuales acerca de los substratos neuronales del condicionamiento pavloviano en los animales y en el hombre. En primer lugar, se resume la investigación sobre condicionamiento en aplysias, que ha demostrado la importancia de la facilitación sináptica amplificada como mecanismo básico del aprendizaje asociativo. A continuación, se describen dos ejemplos de aprendizaje asociativo en vertebrados, el condicionamiento del miedo en roedores y el condicionamiento del parpadeo en conejos, con referencias a la investigación sobre sus substratos neuronales. Se revisa la investigación que muestra el papel de la amígdala en el condicionamiento del miedo y del cerebelo en el condicionamiento del parpadeo, al nivel tanto de circuitos como de la plasticidad celular. Se presta especial atención a los paralelismos que esta área de investigación sugiere entre los mecanismos neuronales del condicionamiento y los principios de las teorías formales del aprendizaje. Por último, se comentan diversas pruebas recientes que demuestran un papel semejante de la amígdala y del cerebelo en el condicionamiento pavloviano humano.
Palabras clave: condicionamiento pavloviano, mecanismos neurales, teorias del aprendizaje

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Pavlovian conditioning is an elemental learning process whose existence has been demonstrated in a wide range of species, both vertebrates and invertebrates. In this basic form of learning, an initially neutral stimulus acquires new behavioral properties due to its pairing in temporal contiguity with an unconditioned stimulus (US). The effects of learning are expressed in the ability of the conditioned stimulus (CS) to elicit motor or physiological reactions adapted to the anticipation of the US and that generally are closely related to the behavior elicited by this stimulus.

The experimental analysis of learning and memory can be undertaken at different, though complementary, levels of analysis, which correspond to different levels of biological organization (e.g., Dudai, 1989). These levels range from the behavioral, whole organism level, to the molecular level. In turn, the neuronal basis of learning and memory have been traditionally studied at three different levels. The first, and more global, is the level of neuronal systems and circuits. The main goal at this level is to delineate the neural systems whose activity is necessary for the learning process to occur and for its results to be stored. A second, cellular level, is aimed at studying learning-induced plasticity processes in the nervous system, lasting alterations of synaptic strength which underlie behavioral change mediated by functional or structural changes in neurons from the systems intervening in learning. Finally, a third, sub-cellular or molecular level, tries to unveil the molecular mechanisms of neuronal plasticity.

The last three decades have witnessed a dramatic advance of the research into the neuroscience of learning and memory and this advance has obviously been more significant in the realm of basic and relatively simple processes of associative and non-associative learning (habituation, sensitization and Palovian conditioning). At present, the behavioral properties of Pavlovian conditioning in several species are reasonably well known (e.g. Rescorla, 1988) and there has been a parallel development of theories analysing its conditions, mechanisms and contents from a cognitive, functional and computational level (e.g., Dickinson, 1980). Intensive behavioral study of some specific exemplars of Pavlovian conditioning in vertebrates and invertebrates has provided a considerable amount of empirical knowledge with a very precise level of detail (e.g. Gabriel, 1988), thus setting the foundations for research in brain and neuronal substrates in a basic form of associative learning. In this brief review, the main results obtained from research into the neuroscience of Pavlovian conditioning will be presented and an effort will be made to establish possible links between the neuronal levels of analysis and the behavioral and cognitive/computational level at which the study of elementary learning processes has been traditionally undertaken.

Pavlovian Conditioning and Neuronal Plasticity in a Simple System: The Case of Aplysia

The concept of learning-related neuronal plasticity refers to the ability of neurons to modify, in a relatively lasting way, their functional and/or structural properties as a consequence of activity induced by a learning experience. The core of learning-induced neuronal plasticity is alteration of the strength of synaptic transmission. The development of a number of model-systems of learning based on Pavlovian conditioning in vertebrates and invertebrates has allowed the study of synaptic plasticity through different neuro-physiological and neuro-chemical indexes. Though several model systems have been developed in invertebrates, such as those of hermissenda (Alkon, 1987), limax maximus (Sahley, 1984) or drosophila (Dudai, 1988), no doubt the best studied example is that of the aplysia, led by Kandel and associates.

Associative and Non-Associative Learning Depend on Changes of Synaptic Efficacy in Reflex Pathways

Numerous studies employing different procedures of associative and non-associative modification of defensive reflexes in aplysia (gill and siphon withdrawal reflexes) have shown that behavioral learning is invariably accompanied by an alteration in post-synaptic potentials (PSP) in sensory-motor synapses. This change in synaptic efficacy is based on the modulation of transmitter release by pre-synaptic cells in pre-established reflex pathways (see Hawkins, Kandel, & Siegelbaum, 1993). While habituation of defensive reflexes involves a decrease of PSP and of transmitter release by the pre-synaptic cell, sensitization conversely involves a strengthening of PSP and an increase in neurotransmitter release (e.g. Castellucci & Kandel, 1974, 1976). Similarly, strengthening of reflex withdrawal reactions to a signal associated with an aversive US by Pavlovian conditioning is accompanied by an increment of PSP in the sensory-motor pathway. The increase of synaptic connections at a superior level to that resulting from non-associative sensitization is strictly dependent on forward CS-US pairing (Hawkins, Kandel, & Siegelbaum, 1983).

Pavlovian Conditioning Depends on Associative-Dependent Amplification of Pre-Synaptic Facilitation

While synaptic depression resulting from habituation is homosynaptic, that is, dependent on repeated activation of the stimulated pathway, synaptic facilitation produced by sensitization and Pavlovian conditioning is heterosynaptic. In this case, facilitation of the sensory-motor synapse is mediated by facilitatory or modulatory interneurons, indirectly excited by the aversive US, that synapse onto the sensory neurons that convey the information of the sensitized stimulus or the CS. A result that has important implications

in the issue of the relationships between learning processes of different levels of complexity, is that Pavlovian conditioning is based on an elaboration of the same mechanisms underlying non-associative sensitization of the reflex (Hawkins, Abrams, Carew, & Kandel, 1983). Both are examples of incremental learning, though the strengthening of the reflex depends on a non-associative procedure in the case of sensitization and of an associative procedure in the case of Pavlovian learning.

Facilitation of the sensory-motor connection is stronger in Pavlovian conditioning and requires that sensory neurons are excited by facilitatory neurons, which use serotonin as a neurotransmitter, after having recently been activated by the CS. Synaptic facilitation by Pavlovian conditioning depends thus on coincidental activity in two neuronal groups, sensory and facilitatory. Moreover, this facilitation requires that activity in these neuronal groups takes place in a precise sequence (sensory neurons must be active before serotonin acts on its receptors), similar to the CS-US sequence which is mandatory for associative behavioral learning. It can thus be said that this coincidence represents neurally the CS-US temporal coincidence, as sensory and facilitatory neurons transmit CS and US information, respectively. The properties of this amplified synaptic facilitation are thus consistent with temporal properties of Pavlovian conditiong such as forward pairing of the CS and US and the effect of interstimulus intervals (Clark, 1984).

In a recent study, Antonov, Antonova, Kandel, & Hawkins (2001) presented decisive evidence of the direct relationship between synaptic plasticity and behavioral associative learning in aplysia. Using a simplified preparation including the siphon, the tail and the nervous system of the aplysia, the conditioning paradigm involved pairing tactile stimulation of the siphon (CS) with a shock to the tail, the CR being siphon withdrawal. Antonov et al. succeeded in showing that activity evoked at siphon sensory neurons and tail motor neurons by the CS changed in parallel to behavioral changes. A greater increase in animals receiving paired, versus those receiving unpaired, trials showed that these changes were associative in nature.

It should be noted that Pavlovian conditioning in aplysia not only involves the strengthening of previously existing responses to the CS, as when an increase in strength or duration of defensive withdrawal is observed. There are demonstrations that alterations in the precise topography of the response to the CS can be induced by Pavlovian learning, so that the response approaches the form of that originally evoked by the UCS itself (e.g., Walters, 1989). This CR specificity seems to be possible due to the fact that synapses of sensory neurons diverge onto different motor neurons and each synapse is modifiable in a specific and indepent way (Martin, Casadio, Zhu, Rose, Chen, Bailey, & Kandel, 1997). This specificity of synaptic connections allows a behavioral change which is specifically adapted to the anticipated US.

Molecular Mechanisms of Associative Neuronal Plasticity

Intracellular mechanisms, on which amplified synaptic facilitation is based, are relatively well known and it is significant that at this level there is still a considerable parallelism with temporal properties of behavioral learning. Action potentials in the sensory neurons seem to increase the sensitivity of the neuron to the action of the facilitatory transmitter (serotonin) released by the facilitatory neurons. One effect of serotonin on the sensory neuron is the activation of the second messenger cAMP (cyclic adenosine monophosphate), which releases a chain of intracellular events through the protein kinase A (PKA). The level of cAMP induced by serotonin at the sensory neuron is further increased if *immediately before* the serotonin pulse, a brief train of action potentials has been produced (Abrams, 1985). When reaching the pre-synaptic terminals of the sensory neuron, the action potential induces a Ca^{2+} influx, which in turn increases cAMP levels through the calcium-calmodulin complex and the enzime adenyl-cyclase. This enzyme, primed by a Ca^{2+} influx, is then more sensitive to the action of serotonin, so that cAMP level, Ca^{2+} influx and, consequently, the level of neurotransmitter released at the terminals of the sensory neuron, are increased. Thus, the requisite of temporal contiguity and forward pairing of the CS and the US for behavioral conditioning has cellular and molecular correlates: paired activity on the sensory neuron and facilitatory neurons and priming of adenyl-cyclase followed by serotonin.

A Second Plasticity Mechanism of Pavlovian Conditioning Follows Hebb's Learning Rule

A second mechanism of neuronal plasticity has been discovered in aplysia's pavlovian defensive learning that involves coincidence of pre- and post-synaptic activity in the sensory-to-motor synapses (Murphy & Glanzman, 1997). This mechanism, similar to long-term potentiation (LTP) studied in the vertebrate brain, is mediated by a sub-class of the receptors of glutamate, NMDA (N-methyl-d-aspartate) receptors and is consistent with Hebb's (1949) learning rule, according to which strengthening of synaptic connections is produced when the pre- and post-synaptic cells fire simultaneously. Activation of the NMDA receptor requires the coincidence of two events: membrane depolarization and binding of glutamate, released at the terminals of the pre-synaptic sensory neuron, to the NMDA receptor at the post-synaptic motor neuron. Activation of NMDA receptors starts a complex chain of molecular events finally leading to a lasting increase of synaptic efficacy in the sensory-motor pathway. This plasticity mechanism has thus associative properties allowing it to act as a detector of the temporal coincidence of CS and

US. However, there are some results which cast some doubts on its role in conditioning in aplysia. For example, temporal properties of LTP in this model-system are not totally consistent with the temporal properties of behavioral learning; though LTP is dependent on pairing of the events it is not sensitive to its precise temporal sequence (Lin & Glanzman, 1997).

Pavlovian Conditioning and Neuronal Plasticity in Vertebrates

While the study of simple invertebrate model-systems of associative learning has provided us with fundamental clues regarding the nature of the processes of learning-related synaptic plasticity and their cellular and molecular basis, research employing Pavlovian conditioning preparations in vertebrates allows an integration of this knowledge into a broader brain systems perspective which is highly relevant from a cognitive and functional point of view. The two best studied exemplars of Pavlovian conditioning in vertebrates are defensive eyelid conditioning (mainly in rabbits) and fear conditioning in rodents. In the first case, a tone (CS) is paired with an airpuff to the eye or periorbital mild shock (US) (e.g., Gormezano, Kehoe, & Marshall, 1983). In fear conditioning, a tone (CS) is paired with a footshosk (US). While in eyelid conditioning the recorded CR is discrete and simple, consisting of the anticipatory eye-blink to the CS, in fear conditioning it is possible to measure a wide range of behavioral, physiological and hormonal changes in response to the CS or danger signal (e.g., Fanselow, 1994).

Fear Conditioning: The Role of Amygdala

There is overwhelming evidence indicating the decisive role of the amygdala in acquisition of conditioned fear. The studies carried out by LeDoux and co-workers (see LeDoux, 2000, for a review) are enormously important. Working at different levels of analysis, from the brain systems to the cellular and molecular levels, these studies have begun to unveil the neuronal substrates of a form of conditioning of immense adaptive significance which generates profound alterations in multiple response systems, from the motor to the physiological and hormonal, and that modulate cognitive processes such as memory and attention.

The procedure employed by LeDoux and co-workers involves pairing of a tone CS and a footshock US. Auditory and somatosensory pathways transmitting CS and US information, respectivey, converge onto the lateral nucleus of the amygdala (LNA), where neuronal responses to both stimuli have been observed (Romanski, LeDoux, Cugnet, & Bordi, 1993). Lesions to different amygdalar sub-nuclei have different effects on fear conditioning (e.g., Maren, 2001). Specifically, lesions to the LNA intereferes with CR acquisition. On the other hand, lesions to the central nucleus of the amygdala (CNA) affect the expression of learning measured through different behavioral, physiological and hormonal indexes. Studies employing pharmacological agents that reversively block the activity of the amygdala have yielded convincing evidence that the role of LNA is specific to the acquisition of the fear CRs, not to its expression (e.g., Wiensky, Schafe, & LeDoux, 1999). The LNA projects through different local pathways to the CNA, which in turn, sends individual projections to different areas controlling different responses; through these areas, the CS is able to elicit alterations of heart rate and other autonomic and hormonal responses, modulate defensive reflexes and elicite defensive motor responses such as freezing. The more popular view is that the LNA is the main role of associative plasticity underlying Pavlovian fear conditioning and that from there information is sent to the CNA, that would act as a system for the control and organization of the complex set of changes which constitute the anticipatory fear response. There are, however, other interpretations that, while not denying the decisive role the amygdala plays in fear conditioning, challenge the assumption that it is the main locus of plasticity (e.g., Cahill, Weinberger, Rozendaal, & McGaugh, 1999).

Fear Conditioning Induces Plastic Changes in Neuronal Responses in the Amygdala and other Areas

Evidence of different kinds suggest that the LNA might be a critical locus for learning the CS-US association during fear conditioning. First, as I have already pointed out, it is where the CS and US pathways converge. Moreover, changes in the response of individual neurons to the CS have been observed as early as in the first conditioning trials. In differential conditioning procedures, using tones of different frequencies as CS+ and CS–, an increase in the response of LNA neurons to the CS+ and a decrease in the response to the CS– has been observed (Maren, Poremba, & Gabriel, 1991). Plastic changes in the reponse to the CS have already been observed in the CNA. However, the temporal properties of these responses are different, the LNA neurons showing short-latency responses (<15 ms from CS onset) and CNA long-latency responses (Quirk, Repa, & LeDoux, 1995), a result which might suggest that plastic changes at the LNA might indicate the start of the neuronal plasticity processes on which the formation of the CS-US association is based. This idea is supported by the fact that in the cited study by Quirk et al., conditioning gave rise to coupling of cell pairs.

Fear conditioning not only induces changes in neuronal response in the amygdala, a structure that seems to be specifically involved in fear and emotional learning. These

changes also occur in cortical and sub-cortical systems mediating perceptual processing. Changes in neuronal response to the auditory CS have been observed in the primary auditory cortex. Specifically, an increase in the response to the specific paired frequency has been observed during acquisition, followed by a decrease during extinction (Diamond & Weinberger,1986).

Moreover, the profile of frequency sensitivity is altered by conditioning so that neurons shift their best frequency in the direction of the paired frequency (Weinberger, 1993; for a review and theoretical analysis, see Weinberger, 1998). These changes are long-lasting, involve an expansion of the cortical representation of the paired frequency and probably reflect, at a functional level, the relevance acquired by the CS+.

Changes in the neuronal response to the CS are also induced in sub-cortical structures. Some studies have indicated the existence of a double sub-cortical pathway for auditory processing, only one of them showing neuronal plasticity. Specifically, the ventral division of the medial geniculate body (MGBv) does not show plasticity, while changes similar to those observed at the cortical level have been detected in the medial division of the MGB, which might thus be considered functionally as part of the neuronal system for learning (Edeline & Weinberger, 1992).

A question that has been amply debated is the relationship between plastic changes in neuronal responses induced by learning in different brain areas, from those involved in early and higher processing of the auditory signal to those that supposedly are specifically involved with the formation of the association. For example, changes in the responses of auditory cortex neurons are already observed after 5 conditioning trials and reach its maximum after 15 trials (Edeline, Pham, & Weinberger, 1993). Moreover, different neuron populations show plastic changes with different temporal properties, with units showing alterations in the early phase of learning and others whose modification has a slower course (Repa, 2001). This observation might be related to the existence of a double pathway of sensory input to the amygdala; a thalamic pathway carrying fundamental processing and a cortical pathway which performs more elaborate processing. This double pathway explains that conditioning with simple tones as CS is possible without the intervention of the auditory cortez (LeDoux, Farb, & Romanski, 1991; LeDoux, Sakaguchi, & Reis, 1984). The thalamus-amygdala pathway provides the amygdala with information processed at a low level and allows rapid learning. There is evidence that the development of neuronal short-latency responses at the LNA depends on this pathway and it has been suggested that neuronal plasticity developed in the auditory cortex might be related to complex processing of the CS (Quirk, Amony, & LeDoux, 1997).

Another related question is the different sensitivity to extinction of the changes in neuronal response observed in these different areas. This is an issue of considerable theoretical interest for behavioral theories of learning, given the abundant evidence that though extinction eliminates the CR, it does not completely abolish the effects of former learning (Bouton, 1993). While there is some evidence showing that plasticity induced in the auditory cortex is reversed by extinction (Diamond & Weinberger, 1986), there are also results indicating that some auditory cortex neurons show plastic changes that persist even after prolonged extinction (Quirk, Armony, & LeDoux, 1997). In a similar way, plasticity induced at the LNA is not always reversed by extinction (Repa, Muller, Aspergis, Desrochers, Zhou, & LeDoux, 2001). In any case, these results clearly indicate that extinction does not abolish all neuronal changes induced by conditioning and are thus consistent with behavioral observations.

Fear Conditioning Induces a Form of Neuronal Plasticity in the Amygdala

The role of the amygdala in storage of fear conditioning experiences is reinforced by studies that have analyzed the relationship between long term potentiation and behavioral learning. On the one hand, pharmacological blocking of NMDA receptors, which mediate LTP, considered to be the main candidate to neuronal plasticity mechanism in the vertebrate brain (e.g., Bliss & Collingirdge, 1993), interferes with fear conditioning (Fanselow & Kim, 1994; Lee & Kim, 1998). Moreover, this relationship is also supported by the fact that behavioral conditioning induces LTP at the physiological level (Rogan, Staubli, & LeDoux, 1997). Another relevant result is that direct administration in the NLA inhibitors of protein synthesis or the protein-kinase A (PKA), treatments that prevent LTP, also interfere with fear conditioning. The effect of these treatments is time-dependent, as they block the formation of the memory trace when administered immediately after conditioning, but not when its application is delayed for 6 hours, thus reflecting a consolidation gradient (Schafe & LeDoux, 2000).

To the extent that LTP is the plasticity mechanism on which the tone-shock association is based, the mentioned results would suggest that plasticity in the LNA codes the associative relationship between the danger signal and the aversive US. LTP might then constitute the mechanism by which the response of LNA neurons to danger signals is strengthened. Functionally, this would amount to an amygdalar representation of the affective value acquired by the CS.

Conditioning of Discrete Motor Responses: The Role of the Cerebellum

A substantial body of research carried out by Thompson and his co-workers has succeeded in

delineating, with considerable precision, the circuit supporting the acquisition of a simple motor CR, the anticipatory eyeblink to a CS signalling an impending aversive US to the eye. Besides tracing the pathways that carry sensory information about the tone CS and the somatosensory US, the output pathways through which the CR is elicited and the possible loci of plasticity, these studies have important functional implications, suggesting a possible neuronal implementation of some learning mechanisms as having been proposed by formal theories of associative learning, mainly the Rescorla-Wagner (RW) model (Rescorla & Wagner, 1972).

Pathways carrying sensory information about the CS and the US converge onto deep cerebellar nuclei and onto the cerebellar cortex. Lesion studies have shown that both acquisition and expression of the eyeblink CR are impeded by small $1mm^3$ specific lesion to the nucleus interpositus (NI) (McCormick & Thomspon, 1984a). Similar results have been obtained in studies employing pharmacological agents that reversibly block NI neuronal activity (Lavond & Steinmetz, 1989). Lesions to the cerebellar cortex do not seem to prevent acquisition, though they do interfere with the precise timing of the CR (e.g., Perret, Ruiz, & Mauk, 1993). A popular hypothesis about the relative contribution of NI and the cerebellar cortex to eyelid conditioning is that while the NI stores the basic memory trace, the cerebellar cortex has a decisive role in adaptation of the CR to the specific temporal CS-US relationship.

Both the NI and the cerebellar cortex show changes in neuronal response to the CS induced by the conditioning protocol. In the course of learning, cells in the NI show an increase in activity that precedes and closely models the behavioral CR (McCormick & Thompson, 1984b). Complementarily, using the procedure of differential conditioned inhibition A+/AX–, where a cue (A, the "conditioned excitor") is paired with the US when presented alone but non reinforced when presented in compound with a second cue (X, the "conditioned inhibitor"), it has been observed that over the development of the A/AX discrimination a differentiation of neuronal responses in the NI emerges, so that activity increases on trials with the excitor alone and decreases on compound trials in the presence of the inhibitor (Freeman & Nicholson, 1999).

A particularly striking demonstration of the role of the cerebellum in the acquisition of the anticipatory eyeblink stems from studies of "neurophysiological conditioning." These studies show that in the total absence of external events, paired stimulation of mossy fibers and climbing fibers, which convey sensory CS and US information respectively and converge at the NI and cerebellar cortex, produces acquisition in a mode similar to the usual behavioral protocol (Steinmetz, Lavond, & Thomspon, 1989).

Sufficiency of the cerebellum for eyelid conditioning depends of the temporal paradigm used. Specifically, delay conditioning, where the US follows immediately after the CS, depends on the cerebellum. However, trace conditioning, where there is a temporal gap separating the CS and the US, also requires the intervention of the hippocampus. Lesion studies have shown that damage to the hippocampus interferes with trace conditioning in rabbits and rats (Weiss, 1999; Solomon, Vander-Schaff, Thompson, & Weisz, 1986).

Two Forms of Synaptic Plasticity Mediate Eyelid Conditioning in the Cerebellum

The results just discussed have promoted the idea that the cerebellum contains the systems where the memory trace codifying the CS-US association is stored. This conclusion is again reinforced by studies that have analyzed learning-related mechanisms of synaptic plasticity in the cerebellum. Two varieties of synaptic plasticity have been described in this structure, LTP in the NI and long-term depression (LTD) at the parallel fibers-Purkinje cells in the cerebellar cortex. This last plasticity mechanism has received much attention as a possible neuronal mechanism of motor learning in the cerebellum (for a recent review of cerebellar plasticity mechanisms see Hansel, Linden, & D'Angelo, 2001).

Cerebellar LTD consists of a lasting decrease of synaptic efficay at the parallel fiber-Purkinje cell connection in the cerebellar cortex. LTP is induced by the pairing of stimulation of the two groups of afferent fibers to Purkinkje cells, mossy-parallel fibers and climbing fibers. This mechanism of decremental plasticity might contribute to Pavlovian learning through disinhibition of neurons of the NI that, as we have seen, seem to be the central role of plasticity. In a study by Chen and Thompson (1995), using an *in vitro* preparation, maximum LTD was observed after stimulation of parallel fibers was preceded by 250 ms stimulation of climbing fibers. These temporal parameters are similar to those effective for behavioral learning or for the neurophysiological conditioning previously described.

A continuously debated question has been the relationship between conditioning-induced neuronal plasticity in the deep cerebellar nuclei and in the cerebellar cortex. Some evidence suggests that cerebellar cortex plasticity must develop first, so that plasticity in NI is then possible. For example, plasticity in the cerebellar cortex is induced before the first CRs are expressed, while plasticity in the NI develops more slowly and parallel to overt performance (Ohyama & Mauk, 2001). Moreover, plasticity in the NI seems to be resistant to extinction, as it has been shown even after 3000 CS alone trials, and it might be related to the faster reacquisition after extinction which is usually obtained with this conditioning preparation (Medina, García, & Mauk, 2001). Based on these kinds of results, some authors have proposed a trigger-storage model of

memory formation during conditioning (Medina, Repa, Mauk, & LeDoux, 2002). This model proposes that different neuron populations in anatomically different loci contribute to the initial induction of learning and to long-term-storage. In eyelid conditioning, Purkinke cells of the cerebellar cortex would be the initiating system, while the NI would be the long-term storage system, where lasting, extinction resistant plasticity, is induced.

Learning as Error Correction: Neuronal Implementations

The main tenet of the most influential theory of associative learning during the last three decades (Rescorla & Wagner, 1972) is that the amount of associative strength (V) acquired by the CS on a trial conditioning trial *i*, (V*i*), is proportional to the difference between the asymptotic level of learning (λ) and the associative strength accumulated to the CS in previous trials:

$$\Delta V_i = \alpha\ (\lambda - V_{i-1})$$

where α is a learning rate parameter related to the salience or associability of the CS.

This model is consistent with several behavioral properties of Pavlovian conditioning. From the standpoint of models such as Rescorla and Wagner's model (RW), learning is viewed as an error-correction process by which discrepancy between the asymptotic level and current associative strength is progressively reduced. In a classical theoretical paper, Hawkins and Kandel (1984) tried to show that not only the most basic properties of Pavlovian conditioning, but also that its higher-order properties, such as stimulus selection with compound CSs and contingency effects, can be implemented on an simple neuronal circuit such as the aplysia´s. However, the most convincing evidence to date of a neuronal implementation of the RW error correction rule comes from studies of eyelid conditioning in rabbits (Gluck & Thompson, 1987; Allen, Myers, & Gluck, 2001; for a review of neuro-computational learning models see Gluck & Granger, 1993).

The CR output pathway in eyelid conditioning is formed by the NI efferents to brain-stem nuclei involved in movement control, such as the red nucleus (RN). Moreover, climbing fibers stemming from the inferior olive send somatosensory information to the cerebellum from the US. Anatomical and physiological studies have shown the existence of an inhibitory pathway from NI to the inferior olive (specifically, the area known as the dorsal accesory olive –DAO–) (e.g., Steinmetz & Sengelaub, 1992). Electrophysiological studies show that, before conditioning, US evoke firing of climbing fibers on CS-US trials. This activity, in turn, induces firing of cortical Purkinje cells. However, this US-evoked activity is dramatically decreased in animals trained at an asymptotic level (e.g., Donegan, Foy, & Thompson, 1985). This decrease is only observed on paired trials, when the US is preceded by an already predictive signal, but not when the US is presented alone, which suggests that the decrease is related to the predictive value of the CS.

Based on these results, the proposal has been made that reduction of US-evoked neuronal activity over the course of conditioning is due to the inhibitory effect exerted by NI on the US pathway. Functionally, this would amount to a progressive reduction in the ability of the US to contribute to the increase of CS associative strength, in a similar way to that which is predicted by the RW model. According to the cerebellar learning model proposed by Gluck, the amount of associative strength accrued by the CS on a given trial is porportional to the level of activation of climbing fibers on that trial. As the CS-US association is strenghtened, the ability of the NI to inhibit activity on the US pathway would increase, with the consequence that the reinforcing ability of the US would progressively decrease until it would become totally ineffective. Consistent with this model, it has been observed that on trials when a well-trained animal shows the anticipatory CR, activity in the DAO is virtually abstent (Sears & Steinmetz, 1991). In other words, US-induced activity at the DAO on a paired trial would constitute a neuronal representation of equal size to the predicitive error. More specifically, DAO activity would be equal to US-evoked activity (λ in the RW model) minus the total associative strength accumulated by the CS up to that trial (V_{i-1} in the model), measured as the activity on the inhibitory NI-DAO pathway.

Extinction and Blocking are also Mediated by the Inhibitory Pathway

Inhibition of DAO and thus of climbing fiber activity seems also to be decisive for extinction to occur. Medina, Nores, and Mauk (2002) have shown that extinction is impeded by the infusion of the GABA ([gamma]-aminobutyric acid) antagonist picrotoxin into the DAO when previously conditioned rabbits received presentations of the tone-CS alone. A computer simulation implemented by these authors (Medina & Mauk, 2000) suggests that both acquisition and extinction of eyelid conditioning requires a departure from the spontaneous level of firing or equilibrium level of climbing fibers. When this level is driven upward by the presentation of the US when it is still not fully predicted by the CS (λ–V positive discrepancy), acquisition occurs. At asymptote, the excitatory effect of the US and the inhibition from the NI-DAO pathway would compensate (no λ–V discrepancy) and no learning would occur. During extinction, inhibition would not be compensated by the US, and DAO activity would be driven downwards. In terms of the RW model, this would amount to a negative λ–V

discrepancy, that is, a negative discrepancy between the "expected" and the actual outcome of the CS, which is precisely the condition the model postulates for extinction to occur.

The blocking effect (Kamin, 1969) is one of the empirical phenomenas that has had the most impact on modern theorizing of associative learning. In the first phase of a blocking experiment subjects receive pairings of a stimulus with a US (A+). In the second phase, a compound of A and a new added cue is paired with the same US (AX+). If in phase 1 stimulus A is conditioned at an asymptotic level, in phase 2 conditioning of X will be blockled; that is, X will not elicit the CR if presented alone. The RW model explains this result through the assumption that when two simultaneously presented cues are paired with a US, the error term results from substracting the sum of associative strength evoked by the compound from λ:

$$\Delta V_i = \alpha\ (\lambda - \Sigma V_{i-1})$$

In Gluck's neuro-computational model, the added element, X, is paired in the second phase of the blocking experiment in the presence of an already predictive cue, A, that inactivates the US through inhibition of DAO activity from the NI. Consistent with this interpretation, it has been shown that reversible inactivation of the NI-DAO inhibitory pathway disrupts the blocking effect in eyelid conditioning (Kim, Krupa, & Thompson, 1998).

The Response of Dopamine Neurons Might Code the Prediction Error in Stimulus-Reward Associative Learning

A comparable function of error signal seems to be performed in other conditioning paradigms by dopaminergic neurons. In studies with monkeys it has been observed that dopamine neurons show short-latency responses to unexpected rewards (i.e., on the first cue-reward pairings). However, this response decreases with training, as the reinforcer, or US, starts to be predicted by the signal-CS and finally comes to be evoked by the signal itself (e.g., Schultz, Apicella, & Lindberg, 1993; Schultz, Dayan, & Montague, 1997; see Schultz & Dickinson, 2000 for a review). Studies employing the bloking procedure have shown that, besides not acquiring control of the CR, the blocked or redundant stimulus never gets to evoke the activity of the dopaminergic neurons (Waelti, Dickinson, & Schultz, 2001).

Pavlovian Conditioning in the Human Brain

There is currently substantial evidence that there are significant similarities between the neuronal substrates of Pavlovian learning in humans and in the vertebrate species most commonly used in animal research. A number of neuropsychological, neurophysiological and brain imaging studies of fear and eyelid conditioning in humans suggest that these forms of conditioning might be mediated by similar brain systems in humans and other vertebrate species.

Conditioned Fear and the Amygdala

There is currently enough evidence implicating the amygdala in fear conditioning in our species (Adolphs, Tranel, Damasio, & Damasio, 1995; Bechara, Tranel, Damasio, Adolphs, Rockland, & Damasio,1995). Bechara et al. have studied acquisition of conditioned fear in three patients with amygdala, hippocampus or amygdala and hippocampus lesions. The authors followed the course of acquisition of both autonomic reactions to a danger signal and explicit or declarative knowledge about the stimulus contingencies. The subject with lesions to the amygdala did not show acquisition of the CR, though he did acquire declarative knowledge of the contingencies. The opposite pattern, that is, CR acquisition but no acquisition of declarative knowledge, was observed in the subject with hippocampal lesion. Finally, the subject with both structures damaged did not show acquisition either of the CR or of declarative knowledge. This a clear example of a dissociation between implicit or non-declarative learning (autonomic activation to the danger signal) and explicit or declarative learning (acquisition of awareness of the contingencies).

Functional magnetic resonance imagery (fMRI) studies have equally shown the decisive role of the amygdala in human fear conditioning (LaBar, Gatenby, Gore, LeDoux, & Phelps, 1995; Büchel, Morris, Dolan, & Friston, 1998). In these studies, differential amygdalar responses were observed to CS+ and CS–. CS-evoked activity was also observed in the anterior cingulate cortex and in both structures a decrease in activation over trials was observed, a result that has been interpreted as reflecting a temporally-limited role for amygdala in acquisition. Another fMRI, differential conditioning study, by Morris, Büchel, and Dolan (2001) has shown that there might be a within-amygdala specialization of different functions involved in conditioned fear acquisition. The fMRI recordings distinguished three different amygdala subregions: the lateral amygdala, where US-evoked responses were observed, the ventral amygdala, which responded to the CS+ and the dorsal amygdala, which showed time-dependent responses to the CS+.

The amygdala seems to have, in our species, a special relevance in other aspects related to the perception of emotional signals, especially those related to threat or danger. fMRI studies have shown that activity specific to the perception of facial expressions of fear is detected in the amygdala (Whalen, Shin, McInerney, Fischer, Wriht, & Rauch, 1998) and in several studies it has been observed that patients with bilateral damage to the amygdala are

impaired in their recognition of fear expressions (Adolphs, Tranel, Damasio, & Damasio, 1994). Insofar as emotional expressions perceived in others may be considered as signals associated with affective consequences, these results are perfectly consistent with those showing the importance of the amygdala in fear conditioning.

A Subcortical Pathway to the Amygdala Might Mediate Response to Masked Danger Signals

Research into the role of the amygdala in fear conditioning has provided results relevant to the issue of the level of processing required for the generation of emotional reactions. As I have already stated, lesion studies in rodents have showed that conditioning with simple tones may proceed without need of cortical input to the amygdala. This learning is mediated by a fast thalamic-amygdalar pathway that conveys auditory information directly to the amygdala (LeDoux et al., 1984, 1991). Information conveyed through this pathway, processed at a low level, allows an immediate reaction that acts as a first line of defense in the face of danger. The existence of this double pathway of sensory input to the amygdala has been considered an important support to the idea that certain components of emotional reactions, namely simpathetic activation, can be elicited without the need of elaborate processing (e.g., Zajonc, 1980) and as a possible neuronal susbtrate for the elicitation of physiological activation by masked danger signals that are not consciously perceived (e.g., Ohman & Soares, 1998).

Some evidence gathered during the last few years is in accordance with the mentioned hypothesis. Morris, Ohman, and Dolan (1998) have shown that stimuli (faces showing a threatening expression) previously paired with an aversive US elicit an amygdalar response even if a masking procedure is used so that the stimuli are not consciously perceived. In fact, the precise locus of activation depended on the presentation mode; non-masked stimuli activated the left amygdala, while masked stimuli activated the right amygdala. This neuronal response to masked stimuli might be mediated by subcortical sensory pathways also in humans. In a PET (positron-emission tomography) study, Morris, Ohman, and Dolan (1999) have provided evidence consistent with this possibility. Activity evoked in the right amygdala to masked fear CSs covariated with activity in the right pulvinar and right superior colliculus, supporting the idea that amygdalar response to masked stimuli was mediated by a subcortical pathway via the thalamus in a similar way to what has been shown in animals.

The Amygdala also Responds to Symbolic Danger

Human amygdala seems to be responsive to different levels of representations of danger, from the most simple based on subcortical inputs to the more complex and cognitive, probably based on higher-order cortical processing. Recently, a role of the amygdala has been shown in the response to stimuli that have been symbolically linked to an aversive outcome. Using an instructed fear conditioning task in an fMRI study, Phelps, O´Connor, Gatenby, Gore, Grillon, and Davis (2001) have shown activation of the left amygdala to visual stimuli that had been verbally related to possible shock administration. This activation was parallel to the expression of fear through skin conductance changes. Given that the shock was really never given, this result shows that the amygdala also has a role in the processing of cognitive representations of danger.

Human Eyelid Conditioning

Studies of eyelid conditioning in humans support, in general, what has been found in other species and confirm the central role of the cerebellum in this form of Pavlovian conditioning. Studies in patients with cerebellar lesions show impaired eyelid conditioning in this population (e.g., Daum, Channon, & Canavan, 1993). Given the finding from animal studies that trace, but not delay conditioning, is mediated by the hippocampus, several studies have studied the acquisition of eyelid conditioning in medial temporal lobe amnesics. These patients acquire eyelid conditioning at a normal rate when a delay paradigm is used (e.g., Weiskrantz & Warrington, 1979). However, acquisition is impaired when a trace paradigm is used and this impairment is more severe the longer the trace interval (McGlinchey-Berroth, 1997). This impairment seems to be specific to the discontinuity between the CS and the US in the trace procedure, given that patients who showed impaired acquisition with a 600 ms trace interval showed, however, perfect conditioning with a 750 ms delay procedure (Gabrieli, McGlinchey-Berroth, Carrillo, & Gluck, 1995). And the role of the hippocampus in trace conditioning is not specific of eyelid conditioning, as it has been confirmed with a different paradigm of aversive conditioning in an fMRI study where increased hemodynamic responses to the trace-CS in the anterior hippocampus was observed.

Delay vs. Trace Conditioning: Implicit vs. Explicit Learning?

The neuroanatomical dissociation of trace and delay conditioning in humans has led some researchers to relate it to the distinction between explicit (or declarative) and implicit (or non-declarative) memory (e.g., Clark, Manns, & Squire, 2002), which are thought to be, respectively, hippocampus-dependent and hippocampus-independent. This distinction is closely tied to the issue of the role of awareness in CR acquisition and there have been several attempts at elucidating the relation between awareness and eyelid conditioning. Though the issue is still controversial and there

are some contradictory results (Knuttinen, Power, Preston, & Disterhoft, 2001), it seems that simple and differential delay conditioning are independent of the development of awareness about the stimulus contingencies. For example, in a study by Clark and Squire (1998) with normal and medial temporal lobe amnesic subjects, normal participants who became aware of the contingencies, conditioned at a similar level to those who did not become aware. A complementary result, also obtained in Clark and Squire's study, is that trace conditioning was strictly dependent on awareness, as acquisition of differential trace conditioning in normal participants depended on awareness. And consistent with the view that the distinction between trace and delay conditioning is parallel to the distinction between explicit and implicit memory, amnesic participants did not become aware of the contingencies and also failed to acquire differential trace conditioning. An unresolved question is the exact relationship between awareness and acquisition in trace procedures, though there is some evidence from studies that have followed trial by trial the development of awareness that it might not have a causal role in the production of the CR (Manns et al., 2000).

Conclusion

The present paper has presented a brief review of the current status of our knowledge of the neural substrates of Pavlovian conditioning at different levels of analyses, from the cellular and sub-cellular to the brain-systems levels and in invertebrate and vertebrate species, including man. Though this knowledge is still fragmentary, much more is known about the neuroscience of Pavlovian conditioning than about any other form of learning and memory. It is encouraging to verify how the intensive study of a simple form of learning at different levels of analysis, from the behavioral to the neural and cognitive-computational, since the time of Pavlov, has contributed to one of the main endeavors of brain and behavior sciences, which is to explain how the brain learns and remembers and how the knowledge acquired through experience governs behavior. We can be sure that Pavlov himself would be pleased to see that the variety of learning he so thoroughly studied and the procedures he developed have greatly contributed to bringing us closer to what was his main research goal, the explanation of brain function, what he called "higher nervous activity," through the interplay between behavioral observation and the direct study of the brain.

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Received July 17, 2003
Revision received September 24, 2003
Accepted October 6, 2003