The biochemistry of memory formation and its regulation by hormones and neuromodulators

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Recent findings have shown that the biochemistry of declarative memory in the areas of the brain involved with its formation and retrieval is strikingly similar to that of long-term potentiation. The memory process, like long-term potentiation, involves a sequence of events that starts by the activation of glutamate receptors, is followed by a variety of enzymatic changes, and involves, some hours after its initiation, gene transcription and protein synthesis. This sequence of events takes place in the hippocampus and, depending on the task, also in amygdala and medial septum and, minutes later, probably in cortical areas of the brain. Peripheral hormones and a variety of brain neuromodulatory systems may enhance or depress different steps of the biochemical sequence. The hormones act in some cases directly on the hippocampus and amygdala (glucocorticoids), and in others (corticotropin, epinephrine) indirectly, through reflex actions on brain neuromodulatory systems (noradrenergic, cholinergic, endorphinergic). The best studied modulatory systems are those related to stress. However, many findings demonstrate a key role in memory modulation of dopaminergic synapses, of brain benzodiazepine-like substances, and perhaps of serotonin acting at specific steps of the biochemistry of memory processes in the hippocampus, amygdala, or elsewhere. Since these systems are involved in the regulation of anxiety and mood, the findings suggest a strong relation between anxiety, mood, and memory, both in normal and in pathological conditions.

Recent data have shown that the biochemistry of the formation and storage of declarative memories involves a cascade of events in specific areas of the brain that is similar to that which underlies long-term potentiation (LTP) in the hippocampus (Baudry & Massicotte, 1992; Izquierdo, 1994; Izquierdo & Medina, 1995; Maren & Baudry, 1995; Medina & Izquierdo, 1995; Reymann, 1993; Sossin, 1996). The biochemical cascade of memory has been best studied in the hippocampus in connection with step-down inhibitory avoidance (Izquierdo & Medina, 1995; Medina & Izquierdo, 1995); many findings suggest that it also occurs in amygdala, medial septum, and entorhinal cortex (Izquierdo, 1994; Izquierdo & Medina, 1995). Involvement of one or another brain area depends on the task. In inhibitory avoidance, all these areas participate in coordinated and/or sequential fashion; in other tasks, like habituation to a novel environment, the amygdala and/or the septum are apparently not involved (Brioni, 1993; Izquierdo, 1994; Izquierdo & Medina, 1995, 1996; Zanatta et al., 1996).

Memory is certainly not formed or consolidated in just one place (Brioni, 1993; Izquierdo, da Cunha, et al., 1992; Izquierdo, Medina, Jerusalinsky, & da Cunha, 1992). Whether it is later stored in restricted areas, particularly for long periods after acquisition (Damasio, 1995; Thompson & Krupa, 1994; Quillfeldt et al., in press), is a matter of debate and intensive current study. The site(s) involved in long-term storage probably vary greatly with the nature of the information being stored, and probably change with time (Quillfeldt et al., in press; Zanatta et al., 1996); these sites will not be discussed here.

Plastic phenomena different from LTP, including long-term depression (LTD; Ito, 1996), may use some of the steps of that biochemical cascade (Rose, 1995; Sossin, 1996). In addition, there are several forms of LTP in which some of the biochemical steps may be different (Nicoll & Malenka, 1995). Further, memory involves modulatory processes that act on several points of the cascade (Bohus, 1994; Izquierdo & Medina, 1995, 1996; Sossin, 1996). Thus, the data that will be discussed here endorse the hypothesis that LTP is a basis of memory, but do not rule out the participation in memory of plastic events other than LTP, and, indeed, suggest that modulatory systems play a crucial role.

The biochemical cascade referred to above involves, first, an activation of AMPA, in most cases NMDA, and in some cases also metabotropic glutamate receptors, followed by pre- and postsynaptic entry of Ca^{++} , which in

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many cases occurs through the channel of NMDA receptors and in others through voltage-dependent Ca^{++} channels (Izquierdo, 1994; Izquierdo & Medina, 1995; Nicoll & Malenka, 1995; Riedel, 1996). This may be coupled with the release of NO, CO, and the platelet-activating factor, which enhances presynaptic glutamate release (see Medina & Izquierdo, 1995). These events are followed by a rapid increase of postsynaptic cyclic guanosyl monophosphate (cGMP) and a slow increase of cyclic adenosyl monophosphate (cAMP; Bernabeu, Schmitz, Faillace, Izquierdo, & Medina, 1996; Huang, Li, & Kandel, 1994), by the pre- and postsynaptic activation of protein kinases A and C and calcium/calmodulin kinase II (Reymann, 1993), and by the phosphorylation of a variety of proteins, including subunits of the NMDA receptor (Koga, Sakai, Tanaka, & Saito, 1996) and the gene transcription factor CREB (cAMP-responsive element binding protein) (Ardenghi et al., in press; Yin & Tully, 1996), among others (Hess, Lynch, & Gall, 1995). Gene activation leads to protein synthesis (Huang et al., 1994), which is necessary for the long-term maintenance both of LTP and of memory (Dunn, 1980; Hess et al., 1995; Huang et al., 1994; Yin & Tully, 1996).

The early events of this cascade (glutamate receptor activation) are blocked by inhibitory GABA_A receptors (Brioni, 1993) and are modulated by cholinergic muscarinic and β -noradrenergic synapses (Izquierdo, da Cunha, et al., 1992; Izquierdo, Medina, et al., 1992). The GABA_A receptors are in turn also modulated by endogenous benzodiazepine-like substances (Wolfman et al., 1991).

Later events (3 or 6 h after the initial activation of glutamate receptors) are modulated by dopaminergic mechanisms, first described by Grecksch and Matthies (1982). In particular, the late protein kinase A/CREB/protein synthesis-dependent phase is modulated by dopamine D₁/D₅ receptors, both in the case of LTP in the hippocampus CA1 region (Huang et al., 1994) and in the case of memory processing by the hippocampus (Ardenghi et al., in press). These later events do not occur if activity of one or another of the protein kinases is inhibited, and abortive forms of LTP and of memory are then seen (Izquierdo, 1994; Izquierdo & Medina, 1995; Reymann, 1993). Protein synthesis inhibitors or the knockout of the genes that encode for some forms of CREB have a similar "abortive" effect on LTP (Huang et al., 1994; Yin & Tully, 1996).

MODULATORY INFLUENCES

In addition to those mentioned above, a variety of central and peripheral modulatory systems have been described that alter memory formation in the immediate posttraining period: Brain β -endorphin and other opioids, cholinergic nicotinic influences, serotonin, peripheral adrenocorticotropin, vasopressin, oxytocin, glucocorticoids, epinephrine, norepinephrine, and glucose (see Bohus, 1994; Cahill & McGaugh, 1996; Gold, 1991, 1995; Grigoryan, Hodges, Mitchell, Sinden, & Gray, 1996;

Izquierdo, 1989; Izquierdo & Medina, 1996; McGaugh, 1989; McGaugh et al., 1995). Most of these substances are in fact released in the brain or outside the brain during many forms of behavioral training (Gold, 1991; Izquierdo, 1989), which signifies that many or most memories are actually formed and often retrieved while under their influence (Izquierdo, 1989; Zornetzer, 1978).

All these hormones and modulators have been shown to have effects on hippocampal LTP, and the effects are of the same sign as those upon memory processes (see Burgard, Cote, & Sarvey, 1991; Gold, Delanoy, & Merrin, 1984; Izquierdo & Medina, 1996; Tyler & DiScenna, 1987). In addition, cholinergic agents alter protein kinase C activity; catecholamines influence cAMP levels and thereby protein kinase A activity; peripherally administered catecholamines influence central catecholamine levels and actions (Gold, 1995; Gold et al., 1984); vasopressin and corticotropin influence brain catecholamine levels (de Wied & Bohus, 1979); and corticotropin, corticosteroids, and opioid agonists and antagonists influence brain norepinephrine effects (Gold, 1991; Izquierdo, 1989; McGaugh, 1989; McGaugh et al., 1995).

Several of the neuromodulatory processes that accompany learning and memory consolidation and retrieval interact with each other. Thus, β -endorphin exerts its generally amnesic (and often state-dependency inducing) effect (Izquierdo, 1989) through influences upon β -noradrenergic and D₂-dopaminergic synapses in the amygdala (McGaugh, 1989) and probably also elsewhere (Izquierdo, 1989); intraseptal infusions of β -endorphin are also amnesic (Bostock, Gallagher, & King, 1988). Cholinergic muscarinic- β -noradrenergic interactions in the amygdala (Dalmaz, Introini-Collison, & McGaugh, 1993; Introini-Collison, Dalmaz, & McGaugh, 1996) and in the hippocampus and septum (see Izquierdo, Medina, et al., 1992) relevant to memory modulation have been described.

There is strong evidence that corticotrophin (Gold, 1991), glucocorticoids (Roosendaal & McGaugh, 1996), vasopressin, and oxytocin (de Wied & Bohus, 1979) cause their effects on memory through interactions with brain noradrenergic mechanisms in the amygdala and hippocampus. There are specific receptors for glucocorticoids in hippocampus, amygdala, and other regions of the brain, however (de Kloet et al., 1991), and abundant evidence indicates that at least part of their effects on memory may be directly through these receptors (de Kloet et al., 1991; McEwen & Sapolsky, 1995; Roosendaal & McGaugh, 1996). Peripherally administered opioids and opioid antagonists alter memory mainly through influences upon the amygdala (McGaugh, 1989; Izquierdo, 1989). Peripheral epinephrine regulates glycemia, and increases in blood glucose mimic the memory-facilitatory effects of epinephrine (Gold, 1995; Gold & McCarty, 1995) and enhance hippocampal LTP (Gold et al., 1984). Hypoglycemia induces synaptic depression in the hippocampus (di Blasi, Fleck, & Barrionuevo, 1995). On the basis of many animal and human data, blood glucose levels have,

in fact, been proposed as a major modulatory factor in memory processes and related neural events (Gold, 1995; Gold & McCarty, 1995).

It is likely that the widespread posttraining changes reported on cyclic nucleotide levels (Bernabeu et al., 1996), protein kinase activity (Bernabeu, Izquierdo, Cammarota, Jerusalinsky, & Medina, 1995), AMPA receptor binding (Cammarota et al., 1995; Tocco et al., 1991), and protein synthesis (Dunn, 1980; Izquierdo et al., 1983) may to a large extent be secondary to effects of the modulatory factors, rather than to synapse-specific, pinpointed events like LTP (Izquierdo & Medina, 1995). In particular, the protein synthesis increase that occurs in several regions of the brain following training procedures can be abolished by adrenalectomy or by adrenal medullectomy and mimicked by corticotropin or by epinephrine (Dunn, 1980; Izquierdo et al., 1983).

It has indeed been suggested that *any* biochemical change that can actually be detected in an autoradiogram or a homogenate or a subcellular preparation from a whole tissue (an entire subarea of the hippocampus, the entire hippocampus or amygdala, etc.) *must* be attributed to modulatory influences (Dunn, 1980), since the changes that would be expected to occur at the particular set of synapses involved in each particular learning experience should be too small to be measurable and would be lost like a needle in a haystack (Dunn, 1980; Izquierdo & Medina, 1995).

Anyway, the fact that modulatory influences can alter the biochemistry of memory at different stages signifies that they may also influence the intensity, duration, or spread of LTP or of other plastic phenomena that use a similar biochemical cascade (see below).

As noted, modulatory influences act in different places of the brain: the hippocampus (Izquierdo, da Cunha, et al., 1992; Izquierdo, Medina, et al., 1992; Gold, 1991, 1995), the amygdala (Cahill & McGaugh, 1990, 1996; McGaugh et al., 1995; Young et al., 1995), the medial septum (Bostock et al., 1988; Brioni, Decker, Gamboa, Izquierdo, & McGaugh, 1990; Izquierdo, da Cunha, et al., 1992; Izquierdo, Medina, et al., 1992), and elsewhere (Damasio, 1995; de Kloet et al., 1991; Gold, 1991, 1995). The relevance of the modulatory influences at each of these regions obviously depends on the type of memory being processed (Brioni, 1993; Gold, 1995; Izquierdo & Medina, 1995). The hippocampus is an obvious site of action for modulatory influences on many types of memory or components of memory: spatial, verbal, and contextual, among others (see Bechara et al., 1995; Izquierdo & Medina, 1995; Izquierdo, Medina, et al., 1992). The amygdala (Bechara et al., 1995; Cahill & McGaugh, 1990, 1996; Izquierdo, da Cunha, et al., 1992; Izquierdo, Medina, et al., 1992; Young et al., 1995) and the medial septum (Davis, 1992; Izquierdo, da Cunha, et al., 1992; Izquierdo & Medina, 1995) are in charge of the emotional, and perhaps especially of the more aversive emotional, aspects of memory. The medial septum is, in addition, involved in spatial memories (Bostock et al., 1988; Brioni et al., 1990). Some data suggest that the main role

of the amygdala would be to actually modulate memories laid down in the hippocampus and other places, particularly the caudate nucleus (Cahill & McGaugh, 1996; McGaugh et al., 1995). The entorhinal and parietal cortex appear to be involved in the late processing of a variety of memories, possibly as an integrator of data previously processed by the hippocampus, amygdala, or septum (Zanatta et al., 1996). Hippocampus, amygdala, septum, and the neocortex are known to receive extensive noradrenergic, dopaminergic, and cholinergic innervation, whose failure has been attributed a role in the genesis of memory disturbances related to aging or to degenerative diseases of the brain, such as Parkinson's or Alzheimer's (Izquierdo & Chaves, in press; Izquierdo, Medina, et al., 1992; Winblad, Hardy, Backman, & Nilsson, 1985).

Since modulatory systems affect the biochemical cascade involved in memory, they may in fact introduce information of their own, and therefore specifically add "colors" or "tinges" to the memories, pertaining to emotional, affective, or related components (Bohus, 1994; Damasio, 1995; Gold, 1995; Izquierdo, 1989, 1994; Izquierdo & Medina, 1995, 1996; Markowitsch, 1994; Zornetzer, 1978). In other words, the biochemical cascade in cells $a \dots n$ in, say, hippocampus, would not be the same as the biochemical cascade stimulated at Step A and B by one neuromodulator, and perhaps inhibited at Step W or Z by another; it would, in fact, store different information (see Izquierdo & Medina, 1996). A large amount of evidence from daily life or clinical studies suggests that this is true (Markowitsch, 1994).

This hypothesis has recently been reiterated with emphasis on the possible influence of modulatory systems on gene transcription (Sossin, 1996). It must be pointed out, however, that all the modulatory systems related to alertness or stress (corticotropin, glucocorticoids, vasopressin, epinephrine, norepinephrine, and central and peripherally acting catecholamine releasers) facilitate memory at low to moderate blood levels or administered doses, but *impair* memory at high levels or doses (Gold, 1991, 1995; Gold & McCarty, 1995; Izquierdo, 1989; McGaugh, 1989). This argues strongly against a direct role on gene transcription, which should presumably follow a linear dose-response curve, and in favor of a mediation of their effects by brain neuromodulators acting synaptically, as has indeed been repeatedly and convincingly demonstrated (see Bohus, 1994; Izquierdo & Medina, 1996; McGaugh et al., 1995). It is common knowledge that low to moderate levels of arousal, or mild anxiety, facilitate learning and retrieval; whereas too high levels of arousal or anxiety (i.e., stress) have an impairing effect (Gold, 1991; Izquierdo, 1989; McGaugh, 1989; Zornetzer, 1978).

THE BIOCHEMICAL CASCADE OF MEMORY FORMATION

Our laboratories and others have studied the biochemical basis of memory formation in detail over the past 5 years. The basic strategy has been (1) to determine the effect on memory of localized infusions into the hippo-

campus, amygdala, or other related brain areas of drugs that selectively act upon the biochemical events of the sequence that underlies LTP (Huang et al., 1994; Reymann, 1993), and the time course of these effects; (2) to investigate the biochemical effects of memory paradigms in the same brain structures, and the time course of these effects. Most of the experiments were carried out using the step-down inhibitory avoidance paradigm, whose pharmacology had been well studied over the years (see Izquierdo, 1989), and which we had recently found to depend on the integrated activity of several brain structures: hippocampus, amygdala, medial septum, and entorhinal cortex (Izquierdo & Medina, 1995, 1996; Wolfman et al., 1991).

The Appendix lists the major findings on the hippocampus, and the notes to the Appendix list the findings in other brain structures.

Some of the drug classes listed in the Appendix have also been studied by systemic injection. Although the results often agree with those of intrahippocampal or intra-amygdala infusions, they are difficult to interpret because of the possibility of multiple side effects, and will not be commented on here; the interested reader is referred to Izquierdo and Medina (1995) or Medina and Izquierdo (1995). Mutant mice lacking one or other glutamate receptor subunit or protein kinase, or CREB, have been produced; when they reach a young adult age, these animals present serious deficits, though not a lack of, hippocampal LTP and hippocampus-based learning (Grant & Silva, 1994). Although the data also generally support the pharmacological findings listed in the Appendix, they must be viewed with care. The gene knockout technique is suited to study the role of (1) given protein(s) in development, but, if animals do survive up to an age of several months, surely they must have generated, through their own development, genetic alternatives to the missing protein(s) (Routtenberg, 1995), especially if these are "housekeeping" proteins such as $GLUR_1$, calcium/calmodulin kinase II, protein kinase C, or CREB. Thus, both systemic drug injection experiments and gene knockout experiments may be viewed as methodologically "dirty." Systemic drug administration is useful when drugs acting on the periphery, or commonly used by systemic administration, or of potential therapeutic value, are tested, but not when mechanisms at a given set of synapses are under investigation. In this sense, obviously microinfusions into restricted brain areas are to be preferred also over intracerebroventricular injections.

The speed at which this field is progressing is illustrated by the fact that in the three most comprehensive reviews published in the past 4 years on correlations between the pharmacology of LTP and that of memory (Baudry & Massicotte, 1992; Izquierdo, 1994; Izquierdo & Medina, 1995), the number of drug classes or pharmacological variables cited was 4, 17, and 25, respectively; in the Appendix and its notes, the number is 39. In the first of those reviews, only one brain structure was included: the hippocampus (Baudry & Massicotte, 1992). A year ago the structures were four: hippocampus, amygdala, medial

septum, and entorhinal cortex (Izquierdo & Medina, 1995). Now there are eight: The striatum, cerebellum, inferior colliculus, and posterior parietal cortex have been added to the list in the past few months.

In spite of the extraordinary degree of coincidence between the findings on LTP and those on learning paradigms, particularly in hippocampus and in relation to inhibitory avoidance, the caveat expressed above concerning the inability to exclude other, parallel or vicarious mechanisms in memory must be kept in mind. First, many of the findings can also be taken to endorse the hypotheses based upon observations in inhibitory avoidance in the chick regarding other forms of plasticity (Rose, 1995; Zhao et al., 1995). Second, Ito (1996) and Tsumoto (1993) have suggested a role for LTD in at least some forms of learning, of which habituation may be part: Indeed, by its very nature (it involves the erasure by phosphatases of whatever protein kinases may be doing in LTP), LTD may well be a natural substrate of forgetting (Tsumoto, 1993). Some of the early steps of LTD (glutamate receptor activation, Ca^{++} entry, protein kinase activation, etc.) are in fact similar to those of LTP, and the switch between LTP and LTD depends on phosphatase activity levels beyond those stages (Ito, 1996). Third, whatever the criticisms, gene knockout experiments may be taken to suggest that some of the steps in the biochemical cascade leading to hippocampal LTP are not essential for LTP, and/or that hippocampal LTP is not an absolute requirement for memory and that alternative mechanisms enter into play in both cases (Grant & Silva, 1994).

Actually, none of these hypotheses is absolutely incompatible with the rest of them. LTP may be in charge of learning in some places and not in others, or some types of learning may require LTP (or LTD) here or there but not elsewhere, or not throughout the entire consolidation period, and so on. Very brief memories, such as those of working memory, might rely on homo- or heterosynaptic facilitation (Izquierdo & Vázquez, 1968), or on other short-lasting combinations of simple, short-lasting electrophysiological events that may (Grant & Silva, 1994) or may not influence LTP or other longer lasting forms of plasticity. Short-lasting or "abortive" LTPs, such as those that take place when protein kinases (Reymann, 1993) or protein synthesis (Huang et al., 1994) are blocked, may play important roles in posttraining memory processes (Jerusalinsky et al., 1994).

It may be naive these days to think that something so basic as learning, which so often looks like what brains are primarily designed to do, should rely on just one mechanism, there being so many possibilities available to nerve cells. This thinking may indeed be as naive as it was to think that some forms of learning rely on just one brain structure (the hippocampus, the cerebellum, the amygdala), as seemed to be the fashion only a couple of years ago. It is now known that even the simplest forms of learning and memory rely on more than one structure. The habituation of exploration of a closed environment requires the hippocampus and the entorhinal cortex, though not the amygdala or septum (Izquierdo,

da Cunha, et al., 1992; Izquierdo & Medina, 1995). Step-down inhibitory avoidance requires the four structures, and subsequently the posterior parietal cortex (Izquierdo, da Cunha, et al., 1992; Izquierdo & Medina, 1995; Zanatta et al., 1996). Eye-blink conditioning is formed in a circuit that involves mainly the cerebellum (Thompson & Krupa, 1994), but is accompanied by changes in AMPA receptor binding in the hippocampus (Tocco et al., 1991) that are very similar to those that have been described for inhibitory avoidance (Cammarota et al., 1995) or LTP (Tocco, Maren, Shors, Baudry & Thompson, 1992). Conditioned startle needs the amygdala, rather than the hippocampus, but requires the activation of a complex circuit as well (Davis, 1992). It can be attenuated by Pavlovian alimentary conditioning, which indicates that very different pathways than those usually employed by this type of learning can be made to functionally converge on them (Schmid, Koch, & Schnitzler, 1995). Separable components of learning tasks are being recognized; and each may require different brain structures and involve different neural mechanisms (Grant & Silva, 1994; Izquierdo & Medina, 1995; McGaugh et al., 1995). Recently, a spatial component of the water maze task insensitive to intracerebroventricular AP5 has been described (Bannerman, Good, Butcher, Ramsay, & Morris, 1995).

CONCLUSIONS, WITH SPECIAL REFERENCE TO MODULATORY PROCESSES

The biochemistry of memory formation in rat hippocampus is now rather well known in relation to inhibitory avoidance learning and, in part, in relation to habituation to a restricted space and a few other tasks, spatial and non-spatial. Some data suggest that a similar biochemical cascade takes place in amygdala and medial septum, at least for inhibitory avoidance, and, starting 30 or so minutes later, in entorhinal cortex. Some findings suggest similar biochemical processes in other brain areas, including the parietal cortex and cerebellum. Neuromodulatory and hormonal events that accompany training procedures may modulate the biochemical cascade at different steps. Peripheral corticotropin, glucocorticoids, vasopressin, and epinephrine have reflex influences on β -noradrenergic synapses in the amygdala, hippocampus, and elsewhere, which interact with cholinergic, β -endorphinergic, and other synapses and modulate the early glutamate receptor-dependent phase of the biochemical sequence of events that underlies memory. This sequence is closely similar to the one that has been described for LTP in the CA1 region of the hippocampus, and with at least most of the events that underlie LTP elsewhere. Somewhere between the 3rd and the 6th h of the cascade, gene activation and protein synthesis appear necessary for both LTP and memory consolidation. In the case of memory and of CA1 LTP, this is strongly regulated by a dopamine D1/cAMP/protein kinase A/CREB-P signaling system. The relation of the

protein synthesis to other, perhaps morphological, more permanent changes, is yet to be studied, both in relation to LTP, which lasts for several weeks (see Izquierdo, 1994, for references), and to long-term memory, which may last for decades.

So far, the best studied modulatory influences on memory, both at the behavioral and at the biochemical level, are those related to stress: the peripheral hypersecretion of corticotropin, vasopressin, corticosteroids, epinephrine, norepinephrine, and glycemia changes, and the central activation of noradrenergic mechanisms (Gold, 1995; Gold & McCarty, 1995; Izquierdo, 1989; McGaugh, 1989; McGaugh et al., 1995). As mentioned above, at low to moderate levels of functioning, these systems facilitate memory formation, whereas at high levels of activity they impair memory (Gold, 1991).

Stress has been repeatedly implicated in the genesis of depression (see Willner, Sampson, Papp, Phillips, & Muscat, 1991) and, of course, of posttraumatic stress disorder. In addition, repeated stress, through a chronic action of glucocorticoids on the hippocampus and other areas involved in memory processing, has been implicated in the direct genesis of cognitive disorders in animals and humans (McEwen & Sapolsky, 1995).

Recent evidence points to memory modulation by neurohumoral mechanisms related to anxiety (brain benzodiazepine-like substances, Wolfman et al., 1991); mood and affect (dopaminergic changes, Ardenghi et al., in press; Izquierdo & Chaves, 1996; changes in serotonin levels, Grigoryan et al., 1996). Serotonin interacts with noradrenergic, dopaminergic, and GABAergic mechanisms in the hippocampus, amygdala, and elsewhere, and its role in the regulation of mood and anxiety levels is thought to derive from these interactions (Graeff, 1993; Grigoryan et al., 1996; Willner et al., 1991). Anxiety and depression deeply affect memory, and it has been suggested that this might be to the dysfunction of serotoninergic, dopaminergic, and GABA_A/benzodiazepine systems (Izquierdo & Chaves, in press). Treatment of depression and, particularly, of posttraumatic stress disorder, involves agents active upon serotoninergic, cholinergic, dopaminergic, and noradrenergic synapses (Friedman & Southwick, 1995).

The study of the influence of modulatory systems on the biochemical chain of events underlying brain plasticity and memory may open the way not only for a better understanding of memory, but also for the treatment of its disorders, and of a variety of brain diseases that are accompanied by disturbed cognition.

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APPENDIX

Several of the LTP-related variables listed below in Table A1 for the hippocampus, as well as a few others, have been studied in other brain structures in various tasks, as follows:

Amygdala. Time course of the effects similar to hippocampus. *Enhancing drugs:* Glutamate, muscarinic agonists, norepinephrine (inhibitory avoidance, Izquierdo, da Cunha, et al., 1992); picrotoxin, 4'-chloridiazepam (inhibitory avoidance, da Cunha et al., 1991); flumazenil (inhibitory avoidance, Wolfman et al., 1991); mc-PAF (inhibitory avoidance, Izquierdo, da Cunha, 1995). *Amnesic drugs:* AP5 (inhibitory avoidance, Izquierdo, da Cunha, et al., 1992; Kim & McGaugh, 1992); AP5 and its heptanoic acid derivative, AP7 (conditioned startle, Miserendino, Sananes, Melia, & Davis, 1990); pretest CNQX (inhibitory avoidance, Izquierdo, da Silva, et al., 1993; conditioned startle (Kim, Campeau, Falls, & Davis, 1993); muscimol (inhibitory avoidance, Izquierdo, da Cunha, et al., 1992); bicuculline (inhibitory avoidance, Brioni, Nagahara, & McGaugh, 1989); benzodiazepines (inhibitory avoidance, Dickinson-Anson & McGaugh, 1993); flumazenil (inhibitory avoidance, Wolfman et al., 1991); CaM II inhibitors (inhibitory avoidance, Wolfman, Fin, Dias, & Bianchin, 1994); PKC inhibitors (inhibitory avoidance, Jerusalinsky et al., 1993); ZnPP (inhibitory avoidance, Bernabeu et al., 1995); BN52021 (inhibitory avoidance, Izquierdo et al., 1995).

Medial septum. Time course of effects similar to hippocampus. *Enhancing drugs:* Glutamate, muscarinic agonists, norepinephrine, picrotoxin (inhibitory avoidance, Izquierdo, da Cunha, et al., 1992); flumazenil (inhibitory avoidance, Wolfman et al., 1991). *Amnesic drugs:* AP5 (inhibitory avoidance, Izquierdo, da Cunha, et al., 1992); CNQX (inhibitory avoidance, Walz et al., 1992); muscimol (water maze, Brioni et al., 1990); inhibitory avoidance (Izquierdo, da Cunha, et al., 1992); flumazenil (inhibitory avoidance, Wolfman et al., 1991).

Entorhinal cortex. Time window of effects, from 30 to 180 min posttraining, and at the time of testing. *Enhancing drugs:* mc-PAF (inhibitory avoidance, Izquierdo et al., 1995). *Amnesic drugs:* AP5 (inhibitory avoidance and habituation, Ferreira, da Silva, Medina, & Izquierdo, 1992; Jerusalinsky, Ferreira, et al., 1992; Zanatta et al., 1996); muscimol (inhibitory avoidance and habituation, Ferreira et al., 1992; Quillfeldt et al., in press); BN52021 (inhibitory avoidance, Izquierdo et al., 1995); CaM II inhibitors (inhibitory avoidance, Wolfman et al., 1994); PKC inhibitors (inhibitory avoidance, Jerusalinsky et al., 1994); CNQX (inhibitory avoidance or habituation, pre-test, Quillfeldt et al., 1994; Quillfeldt et al., in press).

Posterior parietal cortex. Time window, 60-180 min posttraining, and at the time of testing. *Amnesic drugs:* AP5, muscimol (inhibitory avoidance, 60-180 min posttraining, Quillfeldt et al., in press; Zanatta et al., 1996); CNQX (inhibitory avoidance, pre-test, Quillfeldt et al., in press).

Striatum. *Enhancing drug:* mc-PAF (nonspatial water maze task, Packard, Teather, & Bazán, in press). *Amnesic drug:* BN52021 (nonspatial water maze task, Packard et al., in press).

Table A1

Effect of Drugs on Hippocampal Long-Term Potentiation (LTP) and, When Infused Posttraining Into Hippocampus, on Memory of Inhibitory Avoidance (IA), Spatial Habituation (HAB), or Other Tasks; Effect of LTP and of the Tasks on Biochemical Measures Related to LTP

Drug (or Variable)	Time of Administration	Memory				Drug (or Variable)	Time of Administration	LTP	Memory			
		LTP	IA	HAB	Other				LTP	IA	HAB	Other
AP5	early	I	I ¹	I ¹	I ²	mc-PAF	early	E(b)	E ¹⁸	E ¹⁸		
	late	0	0 ³			BN 52021	early	I	I ¹⁸	I ¹⁸		
	expression	0	0 ⁴			BN 52030	early	0	0 ¹⁸	0 ¹⁸		
CNQX	early	I	I ⁵			CaM II inhibitors	early, late (d)	I	I ¹⁹			I ²⁰
	late	I	I ⁶			CaM II activity	early, late (d)	E				E ²⁰
	expression	I	I ^{4,6}	I ^{4,6}		PKC inhibitors	early, late (e)	I	I ²¹			
AMPA receptor B _{max}	early	E(a)	E ⁷		E ⁸	PKC activity	early, late (e)	E	E ²²			
	late	E	E ⁷		E ⁸	PKA inhibitors	late (f)	I	I ²³			I ²⁰
	expression		0 ⁹	0 ⁹		SKF38393	early	0	0 ²³			
GLUR1 levels	early	E	E ¹⁰				late (g)	E	E ²³			
MCPG	early	I	I ¹¹		I ¹²	SCH23390	early	0	0 ²³			
Glutamate	early	E	E ¹	E ¹			late	I	I ²³			
ACPD	early	E(b)	E ¹¹		E ¹²	SCH23390B _{max}	late	E	E ²³			
Muscimol	early	I	I ^{1,3}	I ¹		8-Br-cAMP (f)	early	0	0 ²³			
Picrotoxin	early	E	E ¹	E ¹			late	E	E ²⁴			
Benzodiazepines	early	I	I ¹³	I ¹³	I ¹⁴	cAMP levels (f)	early	0	0 ²⁴			
Muscarinic agonists	early	E(b)	E ¹	E ¹			late	E	E ²³			
Muscarinic antagonists	early	I(c)	I ¹	I ¹		Forskolin	early	0	0 ²³			
Norepinephrine	early	I(b)	E ¹	E ¹			late	E	0 ²³			
N-nitro-arginine	early	I	I ¹⁵			8-Br-cGMP	early	E	E ²⁴			
SNAP (or NO)	early	E	E ¹⁶				late	0	0 ²⁴			
	late		E ¹⁶			cGMP levels	early	E	E ²⁴			
NO synthase activity	early	E	E ¹⁵				late	0	E ²⁴			
ZnPP	early	I	I ¹⁶	I ¹⁶		CREB-P levels	early		E ²³			
Heme-oxygenase activity	early	E	E ¹⁷				late	E	E ²³			

Note—E, Enhancement; I, Inhibition (Amnesia); 0, No Effect. Early, prior to LTP induction or immediately after behavioral training. Late, 30–180 min after induction or training. Expression, prior to the test session. (a) Increased postsynaptic responses to iontophoretic AMPA application. (b) Causes long-lasting potentiation on its own. (c) Blocks potentiation induced by muscarinic agonists. (d) For up to 180 min. (e) For up to 120 min. (f) Starting no less than 30 min and lasting at least up to 180–360 min after LTP induction or behavioral training.

For the data on pharmacology of LTP, see Reymann (1993), Izquierdo (1994), Izquierdo and Medina (1995), Maren and Baudry (1995), and Medina and Izquierdo (1995).

References for the behavioral data are as follows: ¹Izquierdo et al. (1992). ²S. Davis, Butcher, & Morris (1992; spatial learning; intracerebroventricular administration, but AP5 concentrations measured in hippocampus). ³Quillfeldt et al. (in press). ⁴Izquierdo, da Silva, Bueno e Silva, Quillfeldt, & Medina (1993). ⁵Jerusalinsky et al. (1992). ⁶Bianchin et al. (1993). ⁷Cammarota et al. (1995). ⁸Tocco et al. (1991; eye-blink conditioning). ⁹Cammarota et al. (1995). ¹⁰Bernabeu & Medina (in press; western blot). ¹¹Bianchin et al. (1994). ¹²Riedel, Wetzel, & Reymann (1994; spatial learning). ¹³Wolfman et al. (1991; effect of flumazenil). ¹⁴Brioni, Arolfo, Jerusalinsky, Medina, & Izquierdo (1991; water maze). ¹⁵Bernabeu (1995). ¹⁶Fin et al. (1995). ¹⁷Bernabeu, Princ, et al. (1995). ¹⁸Izquierdo et al. (1995). ¹⁹Wolfman et al. (1994). ²⁰Tan & Liang (1995). ²¹Jerusalinsky et al. (1994). ²²Bernabeu, Izquierdo, et al. (1995). ²³Ardenghi et al. (in press). ²⁴Bernabeu et al. (1996).

Cerebellum. cAMP and cGMP level changes after inhibitory avoidance similar and simultaneous to those seen in hippocampus (Bernabeu et al., 1996). *Amnesic drug:* muscimol (eye-blink conditioning, Thompson & Krupa, 1994); *N-nitroarginine*, NO scavengers, inhibitors of protein kinase C, CNQX, MCPG (eye-blink conditioning, Ito, 1996).

Inferior colliculus. *Amnesic drugs:* AP5, ketamine (auditory response alignment, Feldman, Brainard, & Knudsen, 1996).

Substance name abbreviations and nature. AP5, aminophosphonopentanoate, antagonist of glutamate NMDA-type receptors; CNQX, cyanonitroquinoxalinedione, antagonist of glutamate AMPA-type receptors; GLUR₁, a subunit of glutamate ionotropic receptors, essential for LTP; MCPG, methylcarboxyphenyl glycine, antagonist of glutamate metabotropic receptors; ACPD, *trans*-aminocyclopentyl dicarboxylate, agonist at glutamate metabotropic receptors; muscimol, agonist at GABA_A receptors; picrotoxin and 4'-chlorodiazepam, blockers of the ionophore of GABA_A receptors; bicuculline, antagonist at GABA_A receptors; benzodiazepines, positive modulators at GABA_A receptors; flumazenil, benzodiazepine receptor antago-

nist; *N-nitro-arginine*, inhibitor of the enzyme, NO synthase; SNAP, *S-nitroso-N-acetylpenicillinamine*, releaser of NO; ZnPP, zinc-protoporphyrin-9, an inhibitor of heme oxygenase, the enzyme that produces CO; mc-PAF, methyl-carbamyl-PAF or platelet activating factor, a putative synaptic retrograde messenger like NO or CO; BN 52021 and 52030, ginkgolides, antagonists of receptors to PAF located in presynaptic membranes and in microsomes respectively; CaM II, calcium/calmoduline dependent protein kinase II; PKC, protein kinase C; PKA, protein kinase A; SKF 38393, selective dopamine D₁/D₅ receptor agonist; SCH 23390, selective dopamine D₁/D₅ receptor antagonist; cAMP and 8-Br-cAMP, cyclic adenylyl monophosphate and its soluble derivative; cGMP and 8-Br-GMP, cyclic guanylyl monophosphate and its soluble derivative; CREB-P, phosphorylated form of the cAMP-responsive element binding protein, a transcription factor; ketamine, blocker of glutamate NMDA receptor ionophore.