Chapter 3
The Hippocampal Endocannabinoid System in Different Memory Phases: Unveiling the CA1 Circuitry

Jorge Alberto Quillfeldt and Lucas de Oliveira Alvares

Abstract CB1 Cannabinoid receptors are widely expressed throughout the brain, particularly in areas involved in learning and memory, such as the hippocampus. In the CA1 area, they are mainly present at the presynaptic terminals of both GABAergic and glutamatergic neurons. The antagonist/inverse agonist AM251 is a useful pharmacological tool due to its selectivity and ability to tap into the endocannabinoid system (ECS). When infused into the brain, it interferes with the natural functioning of the local pool of endocannabinoids present in each memory phase, and by suppressing the natural course of events, exposes its function in each situation. Anandamide (AEA) was also studied, but results were less consistent. In a large set of experiments spanning several years we have shown that different memory phases are modulated in opposite, complementary ways: AM251 was amnestic (and AEA, facilitatory) when infused into CA1 both after training (consolidation) or after a long reactivation session (extinction), suggesting that ECS modulates positively these phases. On the other hand, AM251 facilitated (and AEA frequently disrupted) memory before test (retrieval) or after a short reactivation session (reconsolidation), suggesting a negative modulatory role. Thus, simmetrically opposed actions are the rule for the ECS in the CA1 area, suggesting both plastic events and complex selective roles taking place under its control, e.g. "switching" between extinction and reconsolidation. Results were interpreted according to known CA1 circuitry and the most probable position of cannabinoid CB1 receptors, pointing to a complex, multifunctional modulatory system that is perfectly consistent with its ubiquity in mammal brains.

Keywords Endocannabinoid system (ECS) · Hippocampus · Memory phases · Memory consolidation · Memory retrieval · Memory extinction · Memory reconsolidation · AM251 · CA1 neural circuit · Switching mechanism

J. A. Quillfeldt (✉) · L. de Oliveira Alvares
Psychobiology and Neurocomputing Lab (LPBNC), Dept. of Biophysics,
IB & Neurosciences Graduate Program, ICBS, Universidade Federal
do Rio Grande do Sul (UFRGS), Porto Alegre, Brazil
e-mail: quillfe@ufrgs.br

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The plant Cannabis has been used by humans for thousands of years for religious, medicinal and recreational proposes [1]. Extensive evidence from animals to humans indicate that cannabinoids affect cognitive performance mainly by modifying the brain endocannabinoid system (ECS) [2]. This endogenous modulatory system is involved in a plethora of physiological functions, including pain, appetite control, motricity, cognition—and one particularly important cognitive function is memory.

ECS is composed by a machinery that involves endocannabinoid ligands, such as anandamide and 2-arachidonoyl glycerol (2-AG), the whole set of enzymes responsible for their synthesis, degradation and reuptake, and the receptors, both canonical (CB1 and CB2), and putative (GPR55, GPR119 and GPR18)—notwithstanding the fact that some endocannabinoids, such as anandamide, can also bind to the transient receptor potential vanilloid 1 cation channel (TRPV1) and other targets [3–7].

Cannabinoid receptors are widely expressed throughout the brain, and noticeably higher levels of CB1 are expressed in brain areas involved in learning and memory, such as the hippocampus and amygdala [8–10]. At the cellular level, CB1 receptors are mainly present at the presynaptic axon terminals of both GABAergic and glutamatergic neurons [11, 12]. Endocannabinoids such as anandamide or 2-AG are synthesized on demand, and released as retrograde messengers from post-synaptic neurons into the synaptic cleft, inhibiting the neurotransmitter release [11, 13].

Ample evidence indicates that either exogenously injected or endogenously released cannabinoids—or their interaction—may have pronounced, yet contradictory effects on learning and memory. In this chapter we will focus on the distinct modulatory roles played by the hippocampal ECS on memory consolidation, retrieval, reconsolidation and extinction.

Temporal Phases of Memory

Memory is a non-instantaneous, complex physiological process that evolves in time—from seconds to minutes, hours, days and even months or years—recruiting different molecular agents in order to produce more or less durable plastic changes in the connections among neural cells of different brain areas, i.e. “recording” the experience in an *engram*. Different phases can be identified according to the temporal position relative to the behavioral experience, and the molecular markers and brain areas engaged [14].

Acquisition

Acquisition, also known as *learning* or *encoding*: takes place during the behavioral experience itself, and integrates information from a whole set of cognitive functions—sensory data, emotional response, attention, motivation, motricity and exploratory strategy [14]. Since each one of those are different functions with different

mechanisms and brain location, treatment before acquisition—"training"—session usually produces results difficult to interpret because it affects several confounding variables, requiring additional control groups.

Consolidation

Right after the acquisition session, memory is labile and can be easily modified by any competitor experience, in which it may be either strengthened or disrupted. The experience begins to amalgamate into a memory trace that stabilizes in a process called *consolidation* [15, 16]. At first the so called *synaptic consolidation* [17, 18] takes place at cellular and subcellular levels, especially in temporal areas such as the hippocampus [19] and the amygdala [20], but also in several cortical areas. After a few weeks, the engram establishes itself in the neocortex in a more persistent way (would this be the real "memory storage"?), becoming less and less dependent on hippocampus—a phenomenon known as *systems consolidation* [18, 21, 22].

Retrieval or Recall

The only actual way to assure that a memory trace was retained is the animal exhibiting a consistent behavioral change in a posterior "test" session [23, 24]. This change must be somewhat measurable, e.g., in an apparatus designed to evince the memory class, be it spatial, emotional/aversive, recognition or appetitive. Retrieval may be tried at any time after training, but if done just seconds or minutes later, it will show only *working memory;* if tests are performed from 2 to 6 h after training, engrams are not considered fully consolidated, and only a *short-term memory* can be expressed; after that, and up to days, weeks or months, a consolidated, *long-term memory* should be accessible. However, even well-consolidated memories will fade away with time, the phenomenon known as *forgetting.*

Post-retrieval Memory Phases

In the recent years it became largely recognized that consolidated traces are not in any sense "unchangeable", but may undergo modifications if some "boundary conditions" are achieved (the right re-exposure time, etc) during its retrieval. Then, a previously consolidated memory may undergo *extinction* (be replaced by a second, different trace that blocks the first) [25] or *reconsolidation* (change its original qualities in different ways, including erasure). Particularly in the case of reconsolidation, the re-exposure to the training context (in the absence of the Unconditioned Stimulus (US—e.g., a shock) seems to destabilize/relabilize the memory trace, that later re-consolidates in a process that is dependent on protein synthesis

[26]. Extinction involves a "consolidation of extinction" phase that also depends on protein synthesis, with a dynamics quite similar to that of a first-time consolidation.

Memory *Consolidation* is Positively Modulated by the ECS in the CA1 Area: the Cannabinoid Antagonist/Inverse Agonist AM251 is Disruptive

Memory consolidation can be selectively targeted in a simple experimental design requiring only one learning trial (e.g., the inhibitory avoidance paradigm in rodents): by injecting/infusing the drug *immediately after training* it is possible to selectively affect the memory consolidation phase, since all the intervening cognitive aspects of learning—attention, motivation, motricity, emotions and information acquisition itself—have been already completed at the time of drug administration. This approach results in "cleaner" interpretation of the obtained data [14], since any observed effect can only be attributed to an interference with whatever takes place in the first hours after training—i.e., the consolidation process [15, 17], avoiding all the other possible confounding variables.

Consolidation plays an important and adaptive role in defining the fate of a memory according to the relevance of its content. For instance, stress hormones released in a threatening situation, such as glucocorticoids or noradrenaline, enhance memory consolidation [27, 28]. The mechanisms behind the memory consolidation processes rely on several cellular and molecular events that occur in brain structures such as the hippocampus. Important steps are the activation of NMDA and AMPA glutamatergic and other metabotropic receptors which leads to an increase of calcium intracellular levels, the consecutive mobilization of a collection of second messengers and the activation of several important enzymes such as PKA, PKC, CAMKII, and MAPK. This will affect both receptors' sensibility and signaling cascades, with some enzymes entering to the nucleus and inducing changes such as the phosphorylation of CREB, promoting gene expression and a change in protein synthesis [17]. In this view, it is important to employ a clear terminology: the endogenous cannabinoid system operates as a *neuromodulatory system*, whose molecular agents perform the fine-tuning of the *effector* excitatory (glutamatergic) and inhibitory (GABAergic) synapses present at the local circuits, resembling, for instance, the operation of the cholinergic, dopaminergic or glucocorticoid systems.

The involvement of the hippocampal endocannabinoid signaling in memory consolidation has been extensively demonstrated, but results may be quite contradictory. Several studies have demonstrated that CB1 receptor agonists impair hippocampus-dependent memory consolidation of inhibitory avoidance, contextual fear conditioning or Morris water maze tasks when injected systemically [29–31] or infused directly into the hippocampus [30, 32]. Moreover, electrophysiological studies show that CB1 receptor activation inhibits long-term potentiation (LTP) induction [33–35].

Our behavioral-pharmacological screening began in 2004–2005, when we first showed that the intra-CA1 infusion of the selective antagonist/inverse agonist[1] AM251, *disrupts memory consolidation* of the Step-Down Inhibitory Avoidance (IA), but not of the Open Field Habituation (HAB), a less aversive task (see Figs 2 and 3 of ref. [36]). This behavioral effect was later confirmed and extended to another aversive task, Contextual Fear Conditioning (CFC) [37].

Learning situations are known to be highly sensitive to a great deal of non-mnemonic factors [34], including animal strain, basal stress levels and/or differences in protocol details, for instance, employed doses, time elapsing between infusion and the task, etc. This is why we carefully controlled for possible locomotor/exploratory unexpected effects in all the above experiments in order to avoid false positives (or negatives) due to behavioural measures misinterpreted for reasons other than mnemonic.

We employed the antagonist/inverse agonist AM251 to interfere with the endocannabinoid system in order to understand its physiological function. Once *selectivity* is the true "Holy Grail" of neuropsychopharmacology, we opted to use AM251, known to be more selective for CB1 receptors than, for instance SR141716A [38–40]. This aspect was further emphasized by the beautiful "U" dose-effect curve we found (see Fig. 2 in ref. [36]), where the maximum effect took place with an intermediate low concentration of AM251, probably the one more selective for CB1 receptors [36].

Notice that AM251, in the exact same concentration found effective on the behavioral experiments, was able to suppress LTP induction in the CA1 region (see Fig. 1 of ref. [41]) in a specially designed ex vivo slice preparation [41].

Consistently with the AM251 findings, we were able to show a weak, yet reproducible *facilitatory* effect of a small concentration of anandamide (AEA) infused immediately after IA training [37]. The effect was absent at higher concentrations, which is consistent with a CB1 receptor-mediated effect. Indeed, anandamide is a poorly selective ligand that can bind to different molecular targets, from the vanilloid TRPV1 receptors [42, 43] to other important targets such as NMDA [44] and muscarinic receptors [45], and possibly also acting as a neurotrophic blocker [46] and/or a modulator of glycine transport [47]. Again, the absence of effect of any drug at higher doses may be explained by its binding to other, "non-specific" sites, where the effect could be different, even opposite to the first one, neutralizing or compensating for it. Being so unspecific, AEA effects may be hard to interpret, except when low doses are used, because binding to lower affinity targets is less probable in this case, favoring activation of the CB1 receptors.

Since neither AM251 nor anandamide were effective when infused before *training* in this task (see Figs. 2 and 3 in ref. [37]), we are confident that, at least in our experimental setup, the CB1-mediated plasticity events underlying memory formation were confined to the post-training, consolidation phase, certainly ignited

[1] AM251 is an inverse agonist [126–129], however, since it also acts as a competitive antagonist displacing endocannabinoids at CB1 receptors and because it is not possible to discriminate between both effects *in vivo* [130], we prefer to classify AM251 as some authors already do, calling it an "antagonist/ inverse agonist".

by the new experience. The absence of pre-training effects contradicted some previous reports [31, 48–50], but considering how hard it may be to separate mnemonic from other cognitive/emotional/motor aspects in this experimental design, we decided not to pursue the *acquisition* avenue much longer.

Taken together, the results with post-training-infused AM251 or AEA in two different aversive (and one non-aversive) tasks suggest that, in the CA1 region of the dorsal hippocampus, memory consolidation mechanisms depend on the integrity of the local endocannabinoid system. The infusion of an antagonist/inverse agonist such as AM251 effectively disrupted the aversive memory, suggesting an action *in the opposite direction of any endogenous agonism*, possibly by blocking the binding of endogenously released cannabinoids to their CB1 targets. The AEA low dose result nicely fits to this suggestion, showing that some exogenously supplemented molecules may be "reinforcing" (within certain concentration limits), possibly by pooling themselves to the endogenously released molecules—the "physiological" pool. There is still no direct proof of endocannabinoids being released in CA1 as consequence of inhibitory avoidance or context fear training, but concentrations of both AEA and 2-AG peaked after a similarly aversive auditory fear conditioning task [72, suppl.]. Also, endocannabinoids were shown to be released in response to stressful/alerting factors at least in the periaqueductal grey substance [50] and the amygdala [9].

A Classical Source of Conflicting Data: Systemic vs. Local Infusions

Some years ago (2004–2005), our findings were *apparently* at odds with the literature, since most authors were used to find just the opposite: amnestic effects with cannabinoid agonists, and facilitatory with antagonists. However, ours was one of the first few works to investigate AM251 effects employing intra-cerebral infusions, i.e. we administrated the drug bilaterally directly into the CA1 area of the dorsal hippocampus, while most of the previous studies employed *systemic* treatments (i.p.). As discussed elsewhere [36, 41] the two approaches should show converging results only if the systemic effect would be relayed by the exact brain structure being targeted, which clearly seems not to be the case here. Indeed, our results strongly suggest that the hippocampus *is not* the mediator of the observed systemic effects. In spite of some evidence supporting the contrary [34], due to the high concentration of CB1 receptors and their dispersion among different brain areas, the systemic effects may probably be the result of a "multitarget" action.

This is not to say that systemic studies are too consistent with the "amnestic-with-agonist/facilitating-with-antagonist" cannabinoid rule: although most agonists exhibit an amnestic effect [34, 51–53], the antagonist/inverse agonist SR141716A (Rimonabant) was shown to produce either facilitatory [53–56] or no effect upon memory [34, 57].

Concerned with this contradictory scenario in those years, we performed some intracerebroventricular infusions of both AM251 and AEA. Our results were very

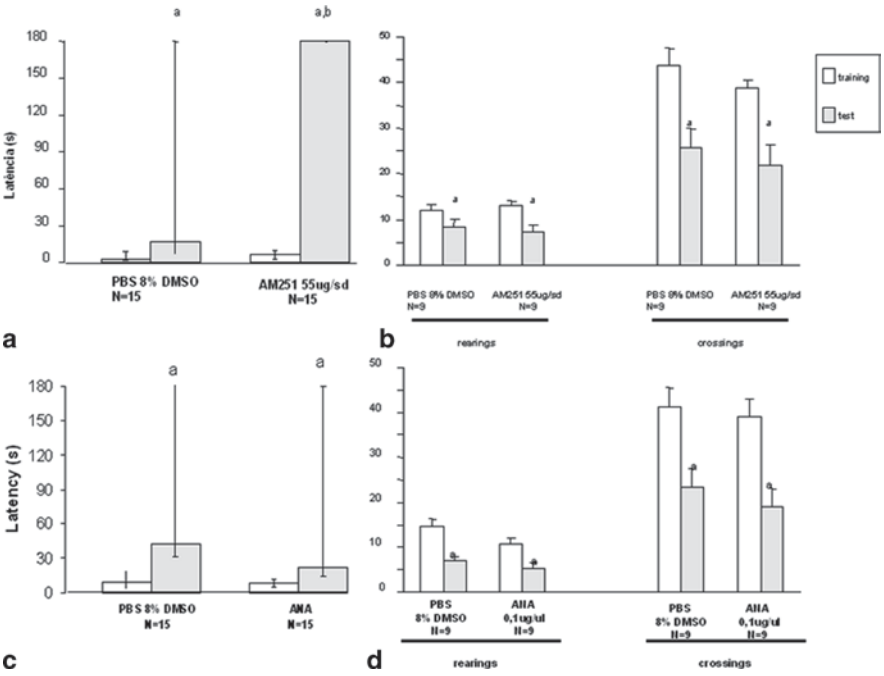

Fig. 3.1 Effect of post-training intracerebroventricular infusions of AM251 (55 ng/uL) or AEA (0.1 ug/uL) upon the performance on IA (**a**, **c**) or HAB (**b**, **d**) tasks. Since IA data (**a**, **c**) were not normally distributed, they were expressed as median (interquartile range) and analyzed with nonparametric statistics (Mann-Whitney for independent groups and Wilcoxon for repeated measures). HAB data were expressed as mean + S.E.M. and analyzed with One-Way ANOVA (independent groups) and Student's t test (dependent groups). **a** Significantly different from training of the same group, $P < 0.05$ (Wilcoxon in **a** and **c**; t test in **b** and **d**). **b** Significantly different from the control group test (Mann-Whitney, $P = 0.015$). Vehicle x Drug test values did not differ significantly between groups in the HAB task for any of the tested drugs (**b** and **d**) and also in the IA task for AEA (**c**)

different from the intra-hippocampal infusions: a significant facilitatory effect of AM251, but not of AEA, upon IA consolidation (none of the drugs caused any effect upon the less aversive task HAB). Notice that, since these IA results did not conform to a normal distribution, they are expressed as median (interquartile range), but regardless of the dispersion in the test groups, the effect was statistically significant (Fig. 3.1).

We brought the above data in support of a principled stand: we should refrain from straightforward comparison of systemic to local infusion results. No matter how important any pharmacological study is, these two approaches carry very different information most of the time. Besides, the more we delve into more anatomically restricted studies in order to understand the exact role of each brain structure and/or neuromodulator system, the less generalizable information becomes. Systemic studies continue to be fundamental, especially when looking for possible clinical applications, but we should be careful to analyze them in the light of intra-

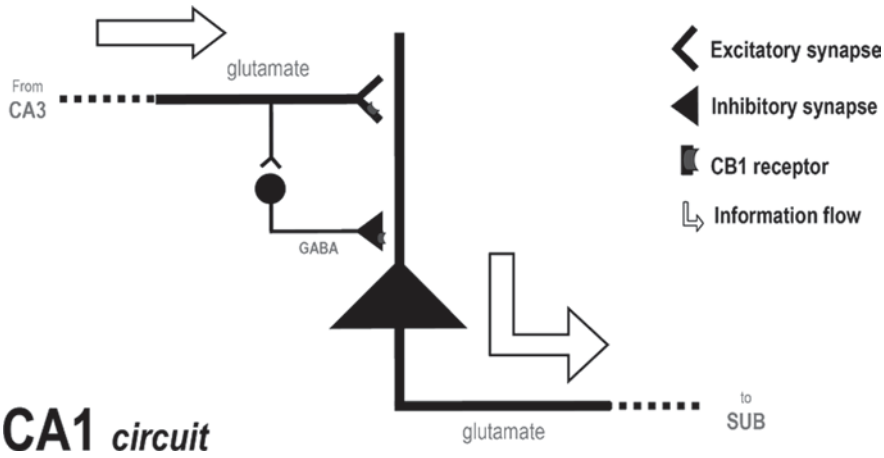

Fig. 3.2 Intrinsic circuitry of CA1 area with CB1 receptor positioned in glutamatergic cells and CCK-expressing GABAergic interneurons. The general hypothesis here is that CA1 glutamatergic efferences are directly involved in the building of the engram. Since there are 20 times more CB1 receptors in the presynaptic terminals of the inhibitory cells than in the excitatory neurons, these CB1 receptors are considered the "target" that explain our results—AM251 amnestic and AEA facilitatory effects

cerebral findings. Hopefully, complex synergic interactions between multiple areas and/or systems seem not to be the rule, otherwise things may be even more complicate experimentally.

Interpreting the Basic Findings According to CA1 Inner Circuitry I: Algebra Doesn't Lie

Since CB1 receptors are present mainly in presynaptic terminals of a subclass (CCK-expressing cells) of the local GABAergic/inhibitory interneurons and, with lower density, in glutamatergic/excitatory "main" neurons [12, 58], we believe it is much simpler to interpret our results in terms of circuitry operation. The trisynaptic circuitry of the hippocampus is well-described since the 60s [59, 60] and brings both frameworks together—CB1 positions upon the trisynaptic circuitry constituting cells, in particular, the CA1 local circuitry including one main excitatory cell and different local interneurons, allowing us to integrate the first findings nicely (Fig. 3.2). The inspiration for this approach comes from the outstanding work of James McGaugh in deciphering the functional (micro)neuroanatomy of the basolateral amygdala, a much more intricate structure, where a putative "circuit" was patiently built over the years through a puzzle-solving strategy that integrated psychopharmacological findings with local infusions of selective drugs [61].

The hippocampal role of these supposedly learning-recruited endocannabinoids is purely speculative at this point: we hypothesize that their endogenous role

Table 3.1 Algebraic model to interpret the present findings in the light of the hypothetical anatomo-functional circuitry depicted in Fig. 3.2

	A	B	C	A X B X C *the* "*algebra*"	
Cell type in CA1	Natural role on engram recording	ECS tonus acting upon this cell[a]	AM251 on CB1 receptors	Memory	LTP
GABAergic interneuron	−	−	−	−	−
Glutamatergic neuron	+	−	−	+	+
Mechanism?	Excitatory/ Inhibitory Action	ECs activate inhibitory CB1 receptors	Antagonists displace ECs or inv.agon. = inv.response		

OBS: + enhancement/facilitation, − inhibition/blocking

[a] same (or absence of) effect obtained by exogenously infused agonist AEA

could modulate the strength of the memory trace (or engram) under consolidation. Endocannabinoids are retrograde messengers released *on demand* that act to decrease the activity of inhibitory networks, which leads to the *disinhibition* of pyramidal neurons [62–65]. These glutamatergic cells project important hippocampal efference putatively involved in feeding the engram formation network, and represent one of the many intra-hippocampal sites where long-term potentiation (LTP) takes place. LTP, or any similar/derived glutamatergic-driven, calcium-dependent process, is a neural plasticity phenomenon long considered a putative mechanism of memory formation [66–69].

The CA1 circuit-based hypothesis is tailored to explain the post-training results, especially the AM251 data, as this antagonist/inverse agonist directly taps into the local ECS, suppressing any natural endogenous functions going on, and thus telling us what might be their nature. An amnestic effect of the antagonist means that the ECS was acting as a natural disinhibitor of local plasticity, since CB1 is an inhibitory G-coupled metabotropic receptor. This is also fully consistent with the observation that endocannabinoids might facilitate hippocampal long-term potentiation through the DSI phenomenon of retrograde inhibition of presynaptic GABA release [70], and in support of that involvement, we have demonstrated that AM251 also suppresses LTP induction in the CA1 region in an *ex vivo* hippocampal slice preparation, with the exact same concentration being effective in the behavioral tasks [41].

Considering that these receptors are located mainly in pre-synaptic terminals of both excitatory and inhibitory cells, in order to interpret the observed drug effects, we will have to resort to some simple algebra (Table 3.1). Considering activation/agonism/facilitation as equivalent to a positive (+) sign, and inhibition/antagonism/amnesia, to a negative (−) one, Table 3.1 synthetizes most of the results covered in this chapter.

Consistency, however, is not enough for a model to be considered proven. Hopefully, the functional circuitry hypothesis depicted in Fig. 3.2 and Table 3.1 seems fully *testable*, something that assures its scientificity. The challenge includes, of course, accommodating also the different findings from other authors.

Notwithstanding the fact that a CB1 receptor-sensitive hippocampal LTP appears to be necessary for the consolidation of the aversive IA memory [41], since AM251 did not affect HAB, LTP seems NOT necessary for the memory consolidation of this less aversive task (see Fig. 3 of ref. [36]), at least in this particular brain region.

Aversive Memory Consolidation Requires a Crosstalk Between Stress Hormones and Endocannabinoids

From the first experiments, it was clear that some degree of aversiveness or alertness was necessary for the cannabinoid drugs to produce any effect, since the Open Field Habituation task (HAB) remained refractory to both AM251 and AEA [36, 41], and the same effects observed in the IA task [36, 37, 41] were also confirmed for CFC [71]. Regardless some reports with knockout (KO) animals on ECS involvement in less aversive situations [72, 73] the aversive/ECS-sensitive-nonaversive/ECS-insensitive pattern was already observed by others [31, 74, 75]. That aversive/emotional aspects play a critical role in memory formation is not a novelty [61, 76–78]. For instance, either corticosterone or stress promote the enhancement of memory consolidation [76, 78]. Another suggestive clue comes from the fact that cannabinoids can influence synaptic events taking place in areas such as the hippocampus, particularly after an aversive stimulation [65, 70]. Finally, several studies demonstrate both the endocannabinoid and the glucocorticoid systems independently improving memory consolidation and suppressing memory retrieval [77, 79], reinforcing the connection that can be either of causality (one promotes the other) or complementarity (one compensates for or substitutes the other).

We then decided to investigate deeper this putative connection between stress and the ECS. The fact that IA and CFC are sensitive to post-training AM251 raises the possibility that the endogenous cannabinoids competing with the antagonist/inverse agonist AM251 were somewhat being recruited by the concomitant stress-related hormones. Indeed, Kamprath et al. [80] have demonstrated that endocannabinoid action depends on the intensity of the footshock in a fear conditioning task that associates tone-response with previous shock treatment. Moreover, several studies prove that both stress and glucocorticoids increase endocannabinoid levels in areas, such as the hypothalamus [81, 82] and the periaqueductal grey matter [50], involved in the fear response. Later, an increase in endocannabinoids released in response to behavioral factors was demonstrated in memory-related areas such as the amygdala [9] and the hippocampus [28, 72], and 2-AG was the main endocannabinoid mobilized in these cases.

In our experiments we did not measure the release of endocannabinoids directly, but managed to approach this possibility in an indirect way. First we showed that CFC memory can be retained after a 0.7 mA, but not a 0.3 mA footshock alone, and that the first result was—exactly like the previous IA consolidation results—reversed by post-training intra-hippocampal AM251 administration. Then we found that the effect of the weak shock was somewhat enhanced by a pre-training procedure,

either a single stress session or an i.p. infusion of the corticosteroid dexamethasone, reaching a freezing level compatible with the one observed with the strong shock. In this case, the response was again blocked by AM251 [27], suggesting that the hippocampal ECS interacts with the glucocorticoid system. Intensity of the stimulus was not the only factor, since both reinforcing procedures were effective when presented immediately, but not 30 min before the training session, a time interval that also fits to the kinetics of corticosterone release [83].

These hippocampal findings are consistent with two similar findings in the amygdala [84, 85]. In the first paper, the memory-enhancing effect of the glucocorticoid system (GCs) was attributed to an ECS-mediated disinhibitory influence on noradrenaline release, a mechanism that facilitated the formation of the aversive memory trace [84, 86]. In the second work, intra-BLA AM251 disrupted the extinction of an avoidance memory, and the agonist WIN55,212–2 (locally or systemically infused) was able to modulate the behavioral enhancement effect of stress, prompting a small increase in plasma corticosterone levels [85]. Thus, not only the dorsal hippocampus and the basolateral amygdala may share an analogous mechanism, but they might even be functionally connected in order to modulate a cognitive process such as the formation of a new contextual fear memory trace [87–89], an important avenue of research still open to contributions.

What is sure to this point is that the activation of the hippocampal ECS requires a certain level of aversiveness in order to exert its modulatory role on fear memory consolidation. The negative emotional state may be provided by [1] the task stimulus itself (e.g., a strong shock), [2] a previous stress session, or, alternatively, [3] the availability of stress hormones such as glucocorticoids. Glucocorticoids may be the putative endogenous mediators of this aversive-dependent hippocampal ECS recruitment, even though it's not clear if this functional link would be taking place in the same or nearby brain structures.

More on the interaction between stress and endocannabinoid modulation of memory can be found in chap. 1 and 5.

Memory Retrieval is Negatively Modulated by the ECS in the CA1 Area: AM251 is Facilitatory

When AM251 was infused before the test session, the effect was exactly the opposite of the post-training one, i.e., we observed a clear-cut *facilitatory* effect on memory retrieval (see Fig. 6 of ref. [37]). AEA, on the other hand, was ineffective. Other authors had also failed to find an effect with AEA [32], possibly due to the low selectivity of AEA as a cannabinoid agonist or to its rapid degradation because of its endogenous nature. Synthetic agonists produce different results; for instance, WIN55,212–2 impaired retrieval when infused into the hippocampus [28]. We should also consider the fact that, for technical reasons, our infusion was made 15 min before test and it is possible that with the longer delay, the

already low dose of exogenous AEA had diffused away and was not effective anymore. Again, additional behavioral tests exclude the possibility of locomotor, non-cognitive actions of the employed pretest concentrations, both for AM251 and AEA. The possibility of a state-dependent phenomenon for AM251 was not fully investigated here.

Although the synthetic cannabinoid agonist WIN55,212–2 did not cause state-dependency [31], this phenomenon has been detected with the infusion of endogenous agonists [90, 91]: the confirmation of an endogenous state-dependency can be understood because AM251 is an antagonist/inverse agonist somehow interfering with the natural functioning of the endogenous pool of endocannabinoids. Independent of any AEA result, we believe the findings of major relevance here are the AM251 effects due to its ability to tap into the ECS.

Memory retrieval is known to share some molecular mechanisms with consolidation—after all, the same cells and brain structures are demanded—but there are also important differences. In particular, retrieval requires neither protein synthesis nor the activation of NMDA receptors and CaMKII, even though there is also a role for CREB phosphorylation [23]. The opposite action of AM251 in memory retrieval vs. consolidation asks for an explanation, and the first thing that comes to mind is that, wherever the drug is acting upon, *something changed*. Thus, following the lead of the circuitry hypothesis outlined above (Fig. 3.2 and Table 3.1), we suppose that some durable changes took place in the CA1 region between the consolidation process and the test moment, that modified the logical attributes of the pharmacological response, changing from disruption to facilitation. Of course, this remains to be proven.

Same Drug, Opposite Effects Demands Explanation: May They Predict Plastic Changes?

At this point, it is interesting to note that while several pharmacological studies show the same effect with the same drug in the two different memory phases described above (see Table 3.2 [92–102]), there is cumulative evidence on the contrary for at least two other important neuromodulatory systems—the cholinergic and the glucocorticoid systems.

Thus, a phenomenon similar to what was found with AM251 was previously described by our lab for a different endogenous modulatory system, the cholinergic system acting though the M4 muscarinic receptors, in the very same structure and behavioral task [92]. The biological nature of such “change” is under investigation in both cases, but we have good reasons to believe they both are of neural circuitry nature, and can be interpreted in the same framework depicted in Fig. 3.2 and Table 3.1. It may well involve either an increased expression of CB1 receptors over the excitatory/pyramidal output pathway as consequence of the learning process—as similarly suggested by ref. [92], or a down-regulation of the CB1 receptors modulating the GABAergic interneurons, or even a combination of such plastic

Table 3.2 Similar vs. opposite effects of drug treatments upon memory consolidation and retrieval phases involving different neurotransmitter and neuromodulator systems[a]

Same treatment, *same* effects			
Treatment		Memory phase	
Drug	Target system	Consolidation	Retrieval
Muscimol (GABA-A agonist)	*GABAergic ($GABA_A$)*	Impairement [93]	Impairement [94]
Nicotine (NAChR agonist)	*Cholinergic (nicotinic)*	Enhancement [95]	Enhancement 95
Scopolamine (MAChR antagonist)	*Cholinergic (muscarinic)*	Impairement [96][b]	Impairement [97]
Noradrenaline (Adrenergic agonist)	*Cathecolaminergic*	Enhancement [98]	Enhancement [99]
Same treatment, *opposite* effects			
MT3 (ACh M4 antagonist)	*Cholinergic (muscarinic)*	Impairement [100]	Enhancement [92]
AM251 (CB1 antagonist/inverse agonist)	*ECS*	Impairement [27 36, 41]	Enhancement [37]
Win55,212-2 (CB1 agonist)	*ECS*	Enhancement [84]	Impairement [102]
RU28362 (GR agonist)	Glicocorticoid	Enhancement [76]	Impairement [79]

[a] A non-exhaustive compilation, only for illustrative reasons. Reference numbers are informed above

[b] The same effect was observed with pirenzepine, a selective muscarinic M1 receptor antagonist, the most common muscarinic receptor and the probable target of less selective muscarinic ligands [101]

events at the same time. Any of these possibilities could equally well explain our results, and fortunately, notwithstanding the technical difficulties, this is a fully testable hypothesis.

In the same sense, both stress and glucocorticoids were shown to promote an analogous response pattern, enhancing memory consolidation and impairing retrieval [79]. Based on this, it has been suggested that the ECS and the glucocorticoid system interact in order to modulate memory retrieval. Indeed, a recent paper has shown that corticosterone increases the endocannabinoids levels in the hippocampus [28], and, complementarily, the local infusion of AM251 into the hippocampus blocks the impairing effect of corticosterone in contextual fear conditioning [102]. Hence, under a stressful situation such as the retrieval of a fear memory, glucocorticoids are released from the adrenal cortex, acting in the hippocampus through the activation of the glucocorticoid receptors that, somehow, induce the synthesis of endocannabinoids that, for their turn, bind to the CB1 receptors, inhibiting the release of neurotransmitters.

Taken together, the *same-drug-opposite-effect* class of pharmacological findings may provide support for a promising circuit-based theoretical framework useful to evince mechanisms behind relevant plastic phenomena related to learning and

memory. Given the fact that Table 3.2 is far from exhaustive, we cannot assure the generality of this phenomenon, but the suggestion is fertile enough to deserve further investigation.

Memory Extinction is Positively Modulated by the ECS in the CA1 Area: AM251 is Disruptive

The extinction phenomenon was first described by Ivan Pavlov, using dogs as subjects [103]. He paired a sound (conditioning stimulus, CS), with the presentation of a piece of meat (unconditioning stimulus, US). The CS alone did not promote any particular response in the animals, however, after being paired with the US, the sound elicits a salivatory response. The prolonged exposure to the conditioned environment without the US led to a gradual reduction of the conditioned response, a process called extinction [25, 104, 105]. In the last decades, memory extinction has been studied by several laboratories, with a dominant use of rodents in fear conditioning to the CS (the context or a tone), with US consisting mostly represented by foot-shocks. In our case, a single, prolonged re-exposure to the context without reinforcement was enough to promote extinction [71].

Thus, when AM251 was locally infused in CA1 after a 25 min re-exposure to the CFC context, fear response in a posterior test was higher than that exhibited by the controls, suggesting that this drug has disrupted the consolidation of extinction [106–108]. Complementarily, intra-hippocampal administration of exogenous AEA has facilitated extinction, an effect reversed by a concomitant sub-effective concentration of AM251 (see Figs. 3 and 6 of ref. [71]). Chhatwal et al. [109] also reported, for Conditioned Fear, a disruption of extinction with the antagonist/inverse agonist SR141716A, and facilitation with the AEA uptake inhibitor and a TRPV1 receptor agonist AM404, that increased the endogenous cannabinoids tonus, an effect then reversed by a concomitant sub-effective concentration of SR141716A. There are other converging studies reporting from extinction attenuation in CB1 KO mice to CB1 receptor blockers disrupting the extinction of a variety of tasks [9, 31, 49, 110, 111]. Although most studies indicate an essential role played by the ECS in memory extinction, its effects seem not to be ubiquitous. There are some types of memory that seem to be independent of CB1 activation, such as those memories with lower levels of aversiveness [36, 41, 74, 75].

The process of fear extinction demands great attention of psychologists and neuroscientists due to its implications in treating PTSD and phobias, as extinction is a core component of most major behavioral-cognitive therapies that approach those devastating, resilient pathologies, despite being plagued by drawbacks like spontaneous recovery and rapid reacquisition. In this scenario, reconsolidation represents new hope, due to its intrinsic qualities whose comprehension is necessary to consolidate it as a promising therapeutically alternative. For more details about the possible therapeutic potential of the endocannabinoid system in PTSD see Chap. 1.

Memory Reconsolidation is Negatively Modulated by the ECS in the CA1 Area: AM251 is Facilitatory

Memory consolidation refers to the gradual stabilization process that occurs after acquisition. Then, when memory is consolidated, it becomes somewhat resistant to interference. However, following retrieval, an already established memory might undergo a labile state again, requiring reconsolidation in order to persist [26]. Reconsolidation is a widespread phenomenon and has been reported in a variety of species and types of memory, indicating that it is a fundamental memory process. The functional role of reconsolidation goes beyond a simple restabilization of the retrieved memory: it allows for memory updating, maintaining its predictive and adaptive relevance. In a recent paper we showed that when memory is reactivated in a situation that does not match the original information, content is qualitatively modified, or "updated"; however, when the contextual condition matches to some extent the original one, memory reactivation operates to either strengthen the trace or maintain the precision of its content over time [112]. Hence, reconsolidation allows for memory modification, such as the integration of new background information into the originally established memory trace.

To this point, data on the effects of endocannabinoid modulation of reconsolidation in the hippocampus region is relatively scarce and controversial. In our experiments AM251 infused intra-hippocampally right after a 3 min re-exposure—a "reactivation" session with the omission of the US—increased the freezing time in the test, implying that memory was labilized and re-consolidated in a *facilitated* form (see Fig. 2 of ref. [71]), an effect that persisted for almost a week. We knew the drug was interfering with reconsolidation because, consistent with previous works of others [26, 110], the suppression of protein synthesis by the transcriptional blocker 5,6-dichloro-1-bold beta-D-ribofuranosylbenzimidazole (DRB) effectively blocked memory expression in the test [113]. This means that a labile state, with its new protein synthesis window of opportunity, was somewhat induced by the reactivation session. Complementarily, AEA *disrupted* memory reconsolidation when infused into the CA1 area, an effect reversible by the concomitant administration of a subthreshold concentration of AM251, in agreement with the idea that the effect was mediated by CB1 receptors (see Fig. 5 in ref. [71]).

The reactivation session was short-lasting, and this time was decisive to define the fate of the memory. None of the treatments affected fear memory when the reactivation session was omitted, meaning not only that *reactivation* was a necessary condition, but that the treatment did not influence fear *per se*.

The disruption of reconsolidation observed with the local infusion of AEA could be alternatively interpreted as a facilitatory effect of AEA upon memory extinction after re-exposure, an effect that could mimic a "reconsolidation disruption". However, this possibility seems unlikely because the response of the control (vehicle-infused) group did not change between reactivation and test sessions (in a real extinction, latencies should decrease). A re-exposure of 3 min only is probably too brief and not "intense" enough to be able to initiate a new memory trace necessary to extinguish the previous one, dissociating CS from the US (see Fig. 2 of ref. [71]).

This argument reminds the classic argument against the existence of reconsolidation as a phenomenon in itself, a flawed criticism in view not only of the two aspects above, but also of the absence of any of other four well known characteristics of an extinction memory, namely spontaneous recovery, rapid reacquisition, renewal, and reinstatement [25].

In apparent contrast to these findings, SR141716A, another CB1 antagonist/inverse agonist, was shown to cause no effect by itself when infused into the hippocampus on memory reconsolidation of two different tasks, but was able to reverse the amnestic effect of the protein synthesis inhibitor anisomycin, suggesting that the CB1 receptor activation has an important role on the destabilization of the memory trace [110, 114]. Importantly, SR141716A is less selective for the CB1 receptor than AM251 [40]. Also, Lin and colleagues [107] has shown that two different CB1 receptor agonists infused in the amygdala impaired reconsolidation, an effect prevented by concomitant administration of AM251. Kobilo et al. [111] also reported that the CB1 receptor agonist WIN55212–2 infused into the insular cortex disrupted memory reconsolidation in the conditioning taste aversion. Recently, Stern and colleagues [115] has shown that the systemic injection of cannabidiol (the main non-psychotomimetic compound of marijuana) was able to disrupt memory reconsolidation in CFC, a hippocampus-dependent task, an effect prevented by co-injection of AM251. Accordingly, De Carvalho and colleagues [116] reported that systemic SR141716A impaired reconsolidation in the morphine-conditioning place preference.

Our results support a role of the dorsal hippocampus ECS in the memory updating process, one of the many demonstrated uses for the process of reconsolidation [112] that allows for the incorporation of new information during a re-exposure/reactivation session.

Opposite Actions of the ECS in Extinction and Reconsolidation: Would ECS be the Switching Mechanism?

Consistently with previous studies, our findings with reconsolidation and extinction showed that the duration of the *reactivation* session is a crucial variable that determines subsequent memory [110, 117, 118]: thus, a brief re-exposure leads to reconsolidation whereas a prolonged reactivation session induces extinction. As commented above, there are relevant functional differences between both processes, reconsolidation being an updating mechanism dedicated to incorporate new information to an already consolidated memory [110, 119], and extinction, the establishment of a new memory that competes with and temporarily suppresses the one formed during the original association [25, 104].

The symmetrically opposed effects of AM251 and AEA in these two post- retrieval phases contrasts with the previous report of Lee et al. 2006 [120] on the role of NMDA in CFC in the very same memory phases. In this study, MK-801 blocked both extinction and reconsolidation, and DCS enhanced both phases in the

same way. As NMDA receptors—besides protein synthesis itself—are key agents sustaining the plastic events behind any new memory formation process, such as "first-time" consolidation, the important results of Lee et al. [120] may imply that they are a necessary component behind the plasticity events necessary either for trace updating (in reconsolidation) or new trace consolidation (in extinction).

ECS modulation, on the other hand, may have a more subtle, differentiated role: by "directly" modulating the effector synapses (by the glutamatergic main cells), or "indirectly" controlling them (through CCK-expressing GABAergic interneurons), this system might act as a selector of the "final" response. Considering the symmetrically opposed effects here described for AM251 and AEA we propose that hippocampal ECS may be acting as a putative *switching mechanism* that decides the fate of a memory trace after its reactivation. This would be the case at least for aversive memories, since there is growing consensus that the ECS needs some stress/glucocorticoids level in order to be recruited [81, 82]. Context matching and time of re-exposure are two important elements to be computed in whatever mechanism exists that determine one or other response, be it reconsolidation or extinction. At this point, however, this is all very conjectural and demands more investigation.

ECS Modulation of CA1 Circuitry in Each Memory Phase: Symmetrically Opposed Actions are the Rule

Table 3.3 summarizes the main findings here reviewed about the observed effects for AM251 and AEA bilaterally infused into the CA1 area of the rat dorsal hippocampus. Except for the pre-training treatment and the infusion without the reactivation session, there is a noticeable pattern of symmetrically opposed actions for each memory phase observed. Remember also that two different aversive tasks were studied here, IA and CFC, and that no effect was ever found in HAB, the only non-aversive task studied.

Our original choice of agonist, AEA, may not have been the best due to the discussed lack of selectivity. However, a low, more CB1 receptor-selective concentration allowed us to observe the asymmetric effects in three of the four memory phases—consolidation, reconsolidation and extinction. In memory retrieval, the *addition* of a low concentration of exogenously infused AEA to the already present endogenous pool of recently-released AEA molecules may have led to two possible situations: either there is not enough AEA in order to reach any effectiveness threshold or, on the contrary, there was too much of it. In this latter case, the extra molecules provided by our exogenous infusion added to the existing pool of AEA may reach a concentration high enough to promote non-specific actions, not mediated by CB1 receptors, which may offset each other and result in no measurable behavioral effects. To decide which of these hypotheses is true, we need to conduct further experiments, either by measuring the amount of AEA locally present, or employing other agonists with a "cleaner" effect. Both possibilities are under scrutiny in our lab.

Table 3.3 A synthesis of our basic findings with AM251 and AEA bilaterally infused into the CA1 area of the dorsal hippocampus in two aversive tasks, IA and CFC, at different stages of memory

Memory phase	CB1 antagonist (AM251– blocks ECS tonus)	CB1 agonist (adds exogenous AEA)	Behavioral task	Ref.
Pre-training (acquisition phase)	Ø	Ø	IA	[37]
Post-training (consolidation phase)	−	+	IA & CFC (AEA in IA only)	[36, 37, 41] (IA) [27] (CFC)
Pretest (retrieval phase only)	+	Ø	IA	[37]
Post-reactivation (of 3 min) (reconsolidation phase)	+	−	CFC	[71]
Post-reactivation (of 25 min) (extinction phase)	−	+	CFC	[71]
No reactivation (neither 3, nor 25 min)	Ø	Ø	CFC	[71]

OBS: − amnestic effect, + facilitatory effect, Ø no observed effect

The problem of adding an exogenous amount of a molecule that exists endogenously and the way they accumulate and/or interact, reminds us of a classic set of findings using beta-endorphin back in the 1980's: the first studies infused a huge amount of substance that was adding to the internal pool to produce one type of effect. However, when the endogenous levels of those opioids were finally measured, much smaller quantities of exogenous substance were infused, and new, unexpected effects, discovered, which later lead to the first demonstration of an endogenous state-dependency [91]. We may be facing the same kind of problem here, which favors the use of different, more selective synthetic agonists.

In an attempt to understand the complexity of AEA effects in the literature, we also performed a set of experiments on the role of TRPV1 receptors in the memory consolidation of two aversive tasks in order to understand something about this "second identity" of AEA as an endovanilloid—as it should be the case under higher concentrations of the ligand. Thus, the TRPV1 antagonist capsazepine was able to impair memory consolidation of both IA and CFC aversive tasks, but the agonist capsaicin, on the other side, had no effect in any of the two tasks [121]. However, the amnestic effect took place only with a strong shock, showing that endovanilloid system also depends on the emotional level in order to be recruited, somewhat resembling the stress-induced recruitment of the ECS. This means that, when studying aversive memories, AEA has "multiple personalities" and may act either as an endocannabinoid (on CB1 receptors) or as an endovanilloid (on TRPV1 receptors), or (more probably) on both targets. So, no easy "separation" is possible, for two reasons: both endogenous systems seem to depend in the same way on the stress level of the task, and, in both cases, AEA physiological action points to a *facilitation* of

the memory consolidation—AEA was facilitatory and AM251 or capsazepine were amnestic post-training. This also suggests that, in terms of memory mechanisms, the endovanilloid system is a modulatory system that somewhat complements the ECS.

Interpreting the Findings According to CA1 Inner Circuitry II: Fitting all the Gang

The cannabinoid antagonist/inverse agonist AM251, when infused into the CA1 hippocampal region, interferes in some way with the natural functioning of the endogenous pool of endocannabinoids present at each memory phase studied here: thus, notwithstanding AEA results, we believe the findings of major relevance here are the AM251 effects due to its ability to *tap into the ECS* and show us exactly what it is doing in every particular moment assayed. To this point, the main empirical conclusions are the following:

- Memory *consolidation* is **positively** modulated by the ECS in the CA1 area, since AM251 was **amnestic**;
- Memory *retrieval* is **negatively** modulated by the ECS in the CA1 area, since AM251 was **facilitatory**;
- Memory *extinction* is **positively** modulated by the ECS in the CA1 area, since AM251 was **amnestic**;
- Memory *reconsolidation* is **negatively** modulated by the ECS in the CA1 area, since AM251 was **facilitatory.**

To these four conclusions, we could add that the ECS in the CA1 area *do not interfere* with memory *acquisition*, since AM251 had not caused any observable pre-training effect in the studied concentration.

From now on, we will be highly speculative. Let's suppose—for the purpose of this model—that only the CA1 area is relevant to decide the fate of a new memory in the whole brain, and that the circuit depicted in Fig. 3.2, and algebraically "explained" in Table 3.1, is a good model to explain those results. Remember that in the "normal" situation, hippocampal CB1 receptors are much more concentrated in GABAergic interneurons than in glutamatergic terminals [11, 12, 122, 123]. We may suggest the following:

- The first conclusion above implies that the targeted CB1 receptors during *consolidation* consist mainly of those present upon the GABAergic interneurons, since, according to our CA1 circuit hypothesis, only in this case an amnestic effect is conceivable;
- If this is correct, the second conclusion could be explained by some plasticity taking place in the CA1 circuitry during *retrieval*, after the memory has been consolidated, with the ECS modulation changed to be more effective on the glutamatergic, excitatory cells (see Table 3.4).

Table 3.4 Fitting the present findings with different memory phases into the algebraic/anatomo-functional circuitry model depicted in Fig. 3.2

	A	B	C	A X B X C *the "algebra"*			
Cell type in CA1	Natural role onengram recording	ECS tonus acting upon this cell[a]	AM251 on CB1 receptors	Memory	LTP	Observed in phase	Switching role?
GABAergic interneuron	−	−	−	−	−	*Consolidation*	*Extinction*
Glutamatergic neuron	+	−	−	+	+	*Retrieval*	*Reconsolidation*
Mechanism?	Excitatory/ Inhibitory Action	ECs activate inhibitory CB1 receptors	Antagonists displace ECs or inv. agon. = inv. response			*Plastic change after learning?*	*ECS assists decision on trace fate?*

OBS: + enhancement/facilitation, − inhibition/blocking

[a] Same (or absence of) effect obtained by exogenously infused agonist AEA

Despite being both testable—however hard this would be—these are two complex and mutually interdependent hypotheses. In this framework, how can we fit conclusions 3 and 4?

- The third conclusion, being qualitatively identical to the first, suggests a similar explanation: it could just be derived from the fact that extinction is the onset of a new memory—despite weaker. Thus, "consolidation of extinction" should naturally share the very same mechanisms of any "first-time" consolidation, including the positive endogenous cannabinoid modulation here verified. It remains to be understood why this new learning ends up being "second class", i.e. subject to such drawbacks as spontaneous recovery, but a strong association with the original memory trace could somewhat help us to solve this riddle;
- Finally, what about the negative ECS modulation of *reconsolidation* inferred in the fourth conclusion? The simplest way to approach this may be to consider it as just a continuation of the retrieval ECS state, since in this case, different plastic mechanisms are being summoned, more or less the same mechanisms specifically involved in the retrieval session.

In an insightful paper of Ivan Izquierdo's Lab concerning memory retrieval [23] it was stated that "the molecular mechanisms that generate extinction are initiated at the time of retrieval in the CAl region of the hippocampus, and include some of those that are involved in retrieval. Therefore, it may be said that retrieval 'plants' the seeds of its own extinction in CA1. Some of the 'seeds' (the MAPK and PKA signaling pathways) are required for retrieval itself; the others (NMDA receptors and CaMKII) are not". This may be true, but we have reasons to suppose that the *seeded* processes should include, above all, those pointing to *reconsolidation*, that

may depend both on the mentioned enzymes *and* on mechanisms more recently proposed as being specifically pertinent to the reconsolidation/updating process underlying an *already-consolidated-just-being-retuned* memory trace, namely those involving L-type VGCCs [114, 124] and the early gene Zif268 [125].

Concerning the dynamical, real life situations, the capacity to update memory seems to be essential for individual survival. The process of reconsolidation might be the most important property of memory, aside from the obvious function of remembering, and understand it is a great challenge to the area of behavioral psychopharmacology in the following years. Table 3.4 summarizes this interpretative scenario.

Concluding Remarks

A substantial amount of research has been undertaken over the past decade reporting the role of the endocannabinoid system on cognitive functions, and it is not possible to adhere to simplifications such as the proposition of ECS as a mere positive or negative modulatory system. There are many factors that can influence the effect of the endocannabinoid on memory, such as the nature of the cognitive task, memory phase moment, drug specificity, context complexity, concentration/dose, level of arousal/aversiveness, and many others. It seems that the endogenous levels of endocannabinoids are fine-tuned to select memory processes in order to warrant regular optimal conditions: the infusion of an extra amount of exogenous cannabinoid, or an antagonist, may break this balance and displace the memory process.

All things taken together, the findings point to a complex, multifunctional modulatory system that performs several functions aimed at shaping the destiny of a memory trace. This would be a good reason for the CB1 receptors to be the most common metabotropic receptors in the brain: they are badly needed to perform such complex switching/directioning functions.

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