Recent advances in the neurochemistry of memory consolidation and retrieval: Impact on current views on memory disorders.

Recentes avanços na neuroquímica da consolidação da memória e evocação: Impacto na concepção atual dos distúrbios de memória.

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ABSTRACT

Many aspects of the molecular basis of declarative memory formation, retrieval and extinction have been established in the past few years. These aspects add to, and partly modify, some long-standing concepts on memory disorders. This article will review data from our laboratories and comment on their impact on these concepts. Particular emphasis will be placed on: a) new findings on the modulation of working memory; b) the separation of short- from long-term memory; c) the molecular pharmacology of memory retrieval.

Keywords: Memory, memory disorders, working memory, short-term memory, long-term memory, retrieval, extinction

Nos últimos anos houve avanços substanciais no conhecimento dos mecanismos moleculares da aquisição, consolidação e evocação das memórias. Muitos desses avanços tem conseqüências importantes na compreensão e no tratamento dos diversos síndromes de déficit de memória (o déficit cognitivo que acontece com a idade avançada, as doenças degenerativas como o síndrome de Alzheimer, etc.). Discutiremos neste artigo os principais avanços na diagnóstico e terapêutica surgidos destes novos conhecimentos sobre a biologia dos processos mnemônicos.

Keywords: Memória, distúrbios da Memória, Memória de trabalho, Memória à curto prazo, Memória a longo prazo, evocação, Extinção.

Memory has long been held to rely on synaptic changes [1,2]. The changes are usually englobed under the term "plasticity". Research on the molecular basis of synaptic plasticity was scanty and inconclusive for decades [3] until the discovery of the phenomenon called long-term potentiation (LTP) in 1973 [4], which consists on the sustained enhancement of synaptic strength by brief tetanic stimulation of the axons afferent to a given synapse. This was the first clear demonstration of a lasting form of neural plasticity that could be measured electrophysiologically. Since then [5-7], there were numerous attempts to equate memory with LTP. The attempts were simplistic and often exaggerated [5,7] and in the '90s it became clear that whereas molecular changes in hippocampal synapses similar to those observed in LTP[7,8,9] take place in the CA1 region of the rodent hippocampus, these changes are far from identical to those of LTP[9]. In addition, the consolidation of several forms of memory in mammals, including in particular fear-motivated memory which has been by far the best studied [9,10], requires not only the hippocampus but also various regions of the cortex, in which the molecular changes that are necessary are different from those seen in the hippocampus, or happen in a different sequence which may not be compatible with LTP [9,11-13].

Another source of neurochemical interpretations of memory is the study of neural correlates of simple

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behaviors in invertebrate models, particularly mollusks [8]. The main and unsurpassable problem of extrapolations from invertebrate models to mammalian memory studies is that the neurotransmitters, neural and metabolic pathways involved are different; so aside from superficial generalizations little can really be transposed from one phylum to the other. To be sure, however, the generalizations are based on coincidences between phases of memory formation and some neurochemical processes involved between mammals and invertebrates [8,14,15]. But, importantly, LTP and mollusk models so far have been applied to the study of just one aspect of memory, namely, its consolidation. Key questions relevant to both the analysis of working and short-term memory, retrieval and extinction remain largely untouched by the LTP and invertebrate models studied so far.

Here we will comment on recent work from our laboratory covering precisely these aspects of memory.

Working memory: Working memory (WM) was viewed until 20 years ago basically as the storage of information relevant to the ulterior successful completion of a behavioral task [16]. As such, it could last for minutes or even hours, and the terms are still sometimes used in this context for the analysis of delayed-matching-to-sample or multitrial maze learning. It was soon understood that WM was different from other forms of short-term memory (STM) and could not be defined as such. For a time, some authors tried to circumvent the problem by developing a concept of several forms of WM, encroaching attentional phenomena, sensory processing and other aspects [17,18]. This concept did not hold, inasmuch as it did not go beyond theoretical postulations and was just an attempt to use an umbrella term for a number of different and disparate processes, whose neural basis was beginning to be uncovered.

The work of Goldman-Rakic and her group restricted the concept of working memory to the type of memory that is active and relevant only for milliseconds or seconds or, at the most, 2 or 3 minutes [19,20]. Thus, she equated WM with immediate memory [21], and visualized working memory as a largely on-line, non-archival set of processes.

The Goldman-Rakic definition of WM is the one that prevails today, and she contributed greatly to this by identifying some of the major neural mechanisms responsible for WM. These are mostly in or around the principal sulcus of the prefrontal cortex and include the integrated activity of on-neurons, off-neurons and neurons that fire between the onset and the offset of stimuli [19,20]. Older data had suggested that the dentate-hippocampus system should also play a pivotal role in WM [16] and Goldman-Rakic was quick to incorporate that work into her framework[19] using metabolic markers such as 2-Deoxyglucose[22] and based on a careful analysis of the interconnections between the prefrontal region and the hippocampus via the entorhinal cortex, and of other transcortical pathways that link the visual system with the prefrontal area[20].

The prefrontal location of a key portion of the WM apparatus is strategic for its role in what many now call the “central manager”, a function somewhat vaguely described as key to decision making based on the linkage of on-going neural activity and pre-existing stored information. A major part of the decision making system of the brain is in the orbitofrontal cortex, with which the remaining prefrontal cortex is connected and which also serves a role in memory formation [23]

Goldman-Rakic and coworkers showed that dopaminergic D1 mechanisms in the prefrontal cortex strongly modulates WM processing [19,20]. We have corroborated this finding and shown that, in addition, D1 receptor agonists and antagonists also regulate WM when given into the CA1 region of the hippocampus, the entorhinal cortex (EC) and the posterior parietal cortex[24]. Further, we showed that local $GABA_A$ receptors inhibit the participation of all these areas in WM, and that intact cholinergic muscarinic receptors in prefrontal cortex, CA1 and EC are necessary for WM. Thus, various neurotransmitters and a wider number of brain regions are involved in WM than hitherto assumed [19,20].

Recent evidence added the basolateral amygdala to the list of brain areas involved in WM. Cholinergic muscarinic[25,26] and nicotinic[27] receptors in this area are required for WM processing in the rat. This adds to the role of cholinergic muscarinic receptors in WM processing in the anterolateral prefrontal cortex. The simultaneous participation of muscarinic and nicotinic receptors [26,27] indicates a wholesale modulatory role for the acetylcholine released in the amygdala by fibers coming from the nucleus of Meynert [24]; much as dopamine, noradrenaline, serotonin and acetylcholine itself have in consolidation[9-11] and retrieval (see below).

WM appears to be critical for decision making (and, of course, for the making and retrieval of memories, see [9,10]). The critical brain area underlying that function has been long proposed to be the orbitofrontal cortex [23], which has strong connections with the rest of the prefrontal region. Perhaps not surprisingly, in view of the recent findings on the role of the basolateral amygdala in WM, this structure has been proposed to play a major role in decision making too [28]. The amygdala is usually

linked to the central control of fear-motivated or otherwise highly alerting or emotional behavior [29,30].

Working memory failure in schizophrenia. Since the pioneering work of Weinberger [31,32], all these recent findings are relevant to the etiology and symptomatology of schizophrenia. This is now viewed basically as a disorder of WM accompanied by deficits in LTM[18,31,33]. The hallucinations that mark this disease are in great part a result of both deficits. Schizophrenics register reality as menacing and confused because their WM is deficient and they cannot usually distinguish one component of the reality they perceive as separate from others, because of a lack of "lateral" inhibition; when exposed, say, to a person leaning on a wall they perceive the person and the wall as a unit, which is of course monstrous and frightening. Then they store the memories thus generated in a deficient LTM system. To be sure, both prefrontal lesions and hippocampal or other temporal lobe lesions are a common finding in schizophrenia [31,33,34]. The lack of "lateral" inhibition among figures or sounds presented simultaneously or in close succession in these patients can be studied by measuring pre-pulse inhibition (inhibition of a regular startle response by a preceding non-startling stimulus)[35]. Since the pathways of startle responses and of pre-pulse inhibition are more or less well known [36,37], there is hope for a better understanding of schizophrenic symptomatology.

The variety and complexity of neurochemical modulation of WM described above, both in the prefrontal cortex and elsewhere, as well as the knowledge that is available nowadays of the modulation of LTM[9,10,11,12,13], may allow for the design of better drugs to treat schizophrenia in the near future. Perhaps the reason why the recently rediscovered "impure" antipsychotics that block not only dopamine D2 but also several other receptors[37], or some of the newer antipsychotics that do likewise, may be the beginning of such new and more efficient therapeutic approaches.

Startle responses can be inhibited by learning procedures [38], and that, if properly used, might eventually be used to overcome the deficit of "lateral" (or pre-pulse) inhibition of schizophrenics. **Short- and long-term memory:** William James**,** in 1890[39]**,** perceived that long-term memories (LTMs) take time to be formed, and proposed that a short-term memory (STM) system should be in charge of remembering while the more definitive trace was being built. McGaugh[40] picked up the subject again in 1966. Since then, it became customary, specially in the United States, to think that STM and LTM were sequential; i.e., that STM is just an early phase of LTM. The vision was challenged by the description of clinical cases of a lack of STM with intact LTM by Warrington and her colleagues in 1969[40].

We figured that the only way to tell whether STM and LTM are sequential or parallel processes in animal models would be to find at least one treatment that abolishes STM while leaving LTM intact for the same task in the same subject. For obvious reasons, the experiment should be pharmacologic; mechanical or genetic treatments would not do, because their duration extends from well before STM to well after LTM testing in any subject in any task. We proceeded to carry out such "STM deletion" experiments [41,42] and in 1998 found several treatments that, when infused immediately post training into either the CA1 region of the hippocampus or the entorhinal cortex, block STM selectively while leaving LTM intact in the same rat for one-trial inhibitory avoidance. Work has gone on since then and we now have at least 11 drugs that do this, plus 19 others that affect STM and LTM differentially[43].

In addition, the studies revealed that the underlying neurochemistry is different for each of these two memory types. In this connection, perhaps the most important finding is that whereas STM requires continuously intact protein kinase A function in the hippocampus during the first 90 min after training, LTM requires that enzyme acting in two peaks, the first at the time of training and in the following 5 min, and the second 180-360 min post training [44], both linked to the phosphorylation of the nuclear transcription factor, cAMPresponsive element binding protein (CREB) [45] and to gene expression and protein synthesis [46]. STM does not require CREB, gene expression or protein synthesis [44,47].

A selective deficit of STM does not occur solely in the patients described by Warrington and Shallice [40]. It is one of the hallmarks of delirium, and it is fairly common in the elderly, particularly those with the so-called mild cognitive impairment. It is also seen in many depressed patients. Such patients often appear in the doctor's office and cannot remember how they arrived there or who brought them, but may recall in detail something that happened yesterday or 20 years ago. In these patients the impairment of STM can be treated by psychotherapy centered in their awareness of the condition, as well as by appropriate anti-amnesic drugs such as gallamine, memantine or the ampakines.

It must be pointed out that for a long time STM was confused with WM (see [17]). The rather precise definition of WM in the terms established by Goldman-Rakic and her coworkers [18,19,21] as a separate, non-archival, mostly on-line, very short-lasting form of memory helped to redefine STM in the terms proposed by James [38] (who called it primary memory) or McGaugh [39] as the form of memory that is operative in the time that it takes for

LTM to be formed. Others have described an intermediate form of memory (ITM) that functions in the period between the duration of STM and the onset of consolidated LTM[47,48]. While evidence in support of an ITM is clear in mollusks, its existence in humans is a matter of debate [49], and is not supported clearly by most clinical research [43].

Retrieval: Curiously, while a large amount of research was carried out on the molecular and systems structure of LTM formation and of STM, the mechanisms of retrieval were largely ignored. Retrieval is, of course, the only way to measure memory [38], and is often the source of many forms of human amnesia.

It has been taken for granted for many years that retrieval of declarative memories depends primarily on the hippocampus (see [17]). Indeed, recent research using imaging methods[50] has shown that the hippocampus plays a major, perhaps a crucial role.

We have studied the molecular pharmacology of retrieval of one-trial avoidance in the rat to some length [51]. It requires intact glutamate receptors in the CA1 region of the hippocampus, the entorhinal cortex, the posterior parietal cortex, the anterior cingulate cortex and the basolateral amygdala, and the activity of protein kinase A and the extracellularly regulated kinase (ERK) pathways in all the structures mentioned except the amygdala[52]. The types of glutamate receptors needed vary with the region studied: AMPA receptors are necessary for retrieval in CA1, entorhinal cortex, parietal cortex and the basolateral amygdala; NMDA receptors are necessary in the parietal and anterior cingulate cortex; mGLuRs are needed in CA1 and in all the neocortical structures. This was established by the infusion of the corresponding antagonists (DNQX, AP5 and MCPG) into the mentioned brain structures 10 min prior to retention testing 24 h after training. The data indicate that retrieval of a simple response such as the one learned in this task requires many brain structures acting in coordinated fashion [51,52] and is therefore a complex and orchestrated event. This is so in spite of the fact that all the molecular mechanisms mentioned are obviously activated instantly, on demand. Animals or humans have no time to develop prolonged metabolic cascades when retrieval is requested from them. In spite of this, biochemical findings show that ERK activity and P-CREB levels in the hippocampus [53] and zif-268 levels in the anterior cingulate cortex [54] increase at the time of retrieval of this or similar fear-motivated tasks.

Current findings do not allow to conclude whether the hippocampus is the “leader” of the orchestra that participates in LTM retrieval, as imaging studies in humans suggest [50]. The zif-268 studies suggest that the anterior cingulated cortex may be the leader [54,55]. It certainly is not the only brain area involved in retrieval. As is known, the hippocampus is strongly connected to the entorhinal cortex and, through it, to all the other areas mentioned [56]. It may well be that different memory types are retrieved by different mechanisms at the systems level.

As we all know from daily experience, mood, surprise, stress and other variables affect retrieval. It has been long known that stress hormones (ACTH, adrenaline, vasopressin, â-endorphin) enhance retrieval[57]; it was recently observed that they do so also in memories acquired a very long time before (3 to 22 months) in rats [58]. The mechanisms are unknown. Exposure to a novel environment or situation also enhances retrieval, in rats and in humans [59]. The effect was, like that of the stress hormones, once attributed to a release of brain â-endorphin [59] but now it appears far more likely that it is linked to activation of PKA and other signaling pathways leading to the phosphorylation of CREB in the hippocampus [60] (see also [53]).

Retrieval failures. As is known, stress or high anxiety hinder retrieval; the effect is due to glucocorticoids released from the adrenal glands and their effects on the basolateral amygdala[61,62]. This explains the failure of retrieval seen in students, actors or teachers who are too anxious or actually stressed at the time in which retrieval of previously well-known memories is demanded from them. The effect of corticoids is opposite to the one they have on consolidation [62] and is not matched by a similar effect of stress hormones [58], unless these are administered at very high doses[57,62].

Mood and emotional states are regulated by central D1-dopaminergic, â-noradrenergic, 1A-serotonin and muscarinic cholinergic receptors in the hippocampus, neocortex and other regions of the brain[11,63]. The corresponding pathways emerge from the substantia nigra, locus ceruleus, raphe nuclei and nuclei of Meynert (see [11,63]). Retrieval is strongly modulated by D1-dopaminergic, â-noradrenergic, 1A-serotonin and muscarinic cholinergic agonists and antagonists infused 10 min before retention testing in CA1, entorhinal cortex, parietal cortex and anterior cingulate cortex [63]. In addition, â-noradrenergic agonists and antagonists also affect retrieval when given into the basolateral amygdala[51,63]. In all cases, D1, â and muscarinic receptors enhance, and 5HT1A receptors impair retrieval [63].

Closing comment. The molecular study of memory formation, including WM, STM and LTM, and of retrieval has changed views on how memory disorders develop

and how they can be treated. This can be applied to both the understanding and treatment of schizophrenia and of many other conditions that are accompanied by, or are due to, memory disorders. In many of these, pharmacologic treatments that specifically influence one or other type or aspect of memory can now be devised, and it is hoped that they will contribute to alleviate the symptomatology of such diseases and conditions. **Acknowledgements.** Work supported by Conselho Nacional de Desenvolvimento Científico e Tecnológico (Brasil) and Agencia para el Desarrollo Científico y Tecnológico (Argentina).

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