The role of the nucleus basalis magnocellularis in fear conditioning consolidation in the rat

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The nucleus basalis magnocellularis (NBM) is known to be involved in the memorization of several conditioned responses. To investigate the role of the NBM in fear conditioning memorization, this neural site was subjected to fully reversible tetrodotoxin (TTX) inactivation during consolidation in adult male Wistar rats that had undergone fear training to acoustic conditioned stimulus (CS) and context. TTX was stereotaxically administered to different groups of rats at increasing intervals after the acquisition session. Memory was assessed as the conditioned freezing duration measured during retention testing, always performed 72 and 96 h after TTX administration. In this way, there was no interference with normal NBM function during either acquisition or retrieval phases, allowing any amnesic effect to be due only to consolidation disruption. The results show that for contextual fear response memory consolidation, NBM functional integrity is necessary up to 24 h post-acquisition. On the other hand, NBM functional integrity was shown to be necessary for memory consolidation of the acoustic CS fear response only immediately after acquisition and not 24-h post-acquisition. The present findings help to elucidate the role of the NBM in memory consolidation and better define the neural circuits involved in fear memories.

The nucleus basalis magnocellularis (NBM) of the rat is homologous to Meynert’s basal nucleus of primates (Wenk 1997). It is located in the ventromedial region of the globus pallidus. This nucleus is a complex and heterogeneous structure of mainly cholinergic neurons, and at least 20%–30% of them are noncholinergic (GABAergic, glutamatergic, and peptidergic) (Detari et al. 1999; Vale-Martinez et al. 2002). The main cholinergic innervation of the cortex, a prevalently ipsilateral and topographic projection, emanates from the NBM. Anterior NBM regions project mainly to frontal and temporal cortices; posterior ones, mainly to the parietal cortex (Saper 1984). The NBM also sends cholinergic projections to other cerebral sites, e.g., lateral and basolateral amygdaloid nuclei (Woolf and Butcher 1982; Schauz and Koch 1999). It has been shown that NBM plays a role in several neural activities (learning, memory, attention, arousal, sleep, sensorimotor integration, locomotion) (Wenk 1997; Wrenn and Wiley 1998; Detari et al. 1999). In particular, the NBM mnemonic role is currently of interest because of the possible involvement of this nucleus in Alzheimer’s mnemonic impairment symptoms (Wenk 1997; Schauz and Koch 1999). In fact, many researchers have attribute the impairments induced by NBM lesions to cholinergic depletion.

In several studies on the NBM role in learning and memory in a variety of learning tasks, electrolytic and excitotoxics lesions were employed (Wenk 1997). The reported deficits support the hypothesis of a role of this neural site in general learning and memory mechanisms (Dunnett et al. 1985; Casamenti et al. 1988; Aaltonen et al. 1991; Schauz and Koch 1999; Gonzalez et al. 2000; Stowell et al. 2000; Moron et al. 2002; Power and McGaugh 2002; Vale-Martinez et al. 2002; Conner et al. 2003; Frick et al. 2004; Knox and Berntson 2006). Nevertheless, it must be underlined that these were permanent lesions. Thus it was impossible to investigate the role played by NBM in the several subsequent stages of the mnemonic process (acquisition, consolidation, retrieval). On the contrary, the reversible functional ablation technique makes it possible to block a brain site during any chosen stage of the mnemonic process, without interfering with the function of the same site during earlier or later processes. As far as we know, the reversible inactivation technique has seldom been employed to investigate NBM mnemonic involvement (Ambrogi Lorenzini et al. 1994; Miranda and Bermudez-Rattoni 1999; Moron et al. 2002). It was shown that NBM is involved in conditioned taste aversion acquisition (Miranda and Bermudez-Rattoni 1999) and in inhibitory avoidance consolidation (Ambrogi Lorenzini et al. 1994; Moron et al. 2002). Ambrogi Lorenzini et al. (1994) reported that tetrodotoxin (TTX) post-acquisition bilateral NBM infusions impaired passive avoidance consolidation when performed up to 48 h after acquisition training. Moreover, even the unilateral blockade of this cerebral site induced consolidation impairment although only during early post-acquisition.

Several conditioning paradigms have been used to investigate the NBM role in aversive conditioning, but classical fear conditioning has been used only in a few studies. In this paradigm, the animal is placed in a conditioning context and a previously neutral stimulus, e.g., a tone (the conditioned stimulus [CS]), is paired with an aversive stimulus such as an electrical footshock (unconditioned stimulus [US]). As a result of the pairing of the tone and context with a footshock, both tone and context are sufficient to elicit a defensive behavioral response (freezing) during re-exposure. Moreover, fear responses to context and to CS may be separately measured (Kim and Fanselow 1992; Sacchetti et al. 1999a,b). Up to now, the role of NBM in mediating fear conditioning is unclear, and especially its role in the consolidation of this aversive behavior is yet to be adequately defined. Although many published reports have analyzed NBM involvement in fear conditioning acquisition (Stowell et al. 2000; Conner et al. 2003; Frick et al. 2004; Knox and Berntson 2006), not much is known about the role played by NBM during fear mnemonic processing that takes place between acquisition and retrieval, i.e., during consolidation, when the mnemonic trace changes from short-term to long-term to be subsequently stored (Frick et al. 2004).

The aim of the present work was to obtain information on the role of NBM during consolidation of the conditioned freezing response to the CS and context. NBM was reversibly unilaterally
and bilaterally inactivated by the stereotaxic administration of TTX (Fig. 1) performed at increasing post-acquisition delays in rats that had undergone fear conditioning to acoustic CS and to context.

Results

During the single acquisition training session, spontaneous behavior was homogeneous in rats of all eight groups. Locomotory and explorative behavior was the same in all groups during the initial 3-min free exploration period (11%–16% immobility of the total exposure time). A very long freezing duration was exhibited by the rats of all groups during the 2-min post-shock period in the conditioning chamber. The mean freezing duration of the eight groups ranged between 77.5 and 85.4% of total time (Fig. 2). One-way ANOVA showed that there were no significant differences between groups (F (2, 122) = 5.97, P < 0.01) and among responses, treatment, and time lapsed in the context. Differences were not statistically significant with mixed ANOVAs (2 × 2) showing statistically significant differences only between responses (F (1, 122) = 8.36, P < 0.01) but not between treatments (F (1, 122) = 0.32, P = NS) after NBM reversible inactivation, context freezing re- sponse and between T-0.25 (P < 0.01) and T-24 (P < 0.05) groups and the respective controls (S) for freezing response to conditioning context and between T-0.25 and S-0.25 for acoustic CS freezing response (P < 0.01) (Fig. 3). The freezing duration during the first 3 min of retention testing in the new context without CS presentation ranged between 16.5 and 18.1% of total time (Fig. 4) in the six groups. One-way ANOVA showed that there were no significant differences between groups (F (6, 61) = 0.29, P = NS), thus demonstrating that NBM inactivation did not determine generalization phenomena.

Unilateral inactivation

Figure 5 shows that NBM unilateral TTX inactivation impaired consolidation of the freezing response neither to acoustic CS nor to context. Differences were not statistically significant with mixed ANOVAs (2 × 2) showing statistically significant differences only between responses (F (1, 44) = 8.36, P < 0.01) but not between treatments (F (1, 44) = 0.32, P = NS).

Discussion

The present findings show that NBM is fully involved in conditioned fear responses consolidation. Post-acquisition bilateral NBM inactivation affects freezing response both to acoustic CS and to context, although not with the same post-acquisition delays. NBM functional integrity appears to be necessary up to the 24-h post-acquisition delay for context conditioning. On the other hand, NBM functional integrity appears to be necessary only during the earlier post-acquisition times for acoustic CS conditioning. We also demonstrate that NBM unilateral blockade did not impair the memorization of either response even if performed immediately after acquisition.

Methodological considerations

In the present paradigm, freezing is a conditioned (learned) response. The experimental subjects did not exhibit freezing when

![Figure 1.](image1)

**Figure 1.** Injection sites in nucleus basalis magnocellularis (NBM) (arrows indicate end of needle tracks).

**Figure 2.** Freezing reaction to fear conditioning training. Mean ± SEM freezing as percentage of total time in the 2-min period after last shock during fear conditioning acquisition training. (For details, see Materials and Methods.)
placed in the conditioning apparatus prior to the training session (Corodimas and LeDoux 1995; Sacchetti et al. 1999a, 2001, 2002; Baldi et al. 2007). After the single training session, freezing responses appeared only following the presentation of previously administered stimuli (acoustic CS and context). During retrieval testing sessions, up to when CS and context were not presented again, freezing durations, if any, were very short. This result shows that the generalization phenomenon was absent (Fig. 4; Corodimas and LeDoux 1995, Sacchetti et al. 1999a,b, 2002, 2003; Baldi et al. 2007).

Immediately after conditioning, the freezing behavior of all eight groups of experimental animals (Fig. 2) showed a homogenous response to shocks. Moreover, during retrieval testing, the very good conditioned freezing response both to acoustic CS and to context exhibited by all S control groups (Fig. 3) was quite similar to that previously reported (Sacchetti et al. 1999a,b, 2002, 2003; Baldi et al. 2004, 2007). It may be concluded that the shorter freezing response of TTX-injected rats is due to the amnesic effect of the NBM inactivation performed during consolidation. As previously stated, only a single training session acquisition paradigm permits a chronological analysis of the involvement of a given neural structure in memory consolidation. This because the starting time of mnemonic processing is thus exactly defined, while such an exact definition is not possible in the case of repeated acquisition-session paradigms (Ambrogi Lorenzini et al. 1994). This paradigm is indeed thought to be sufficiently similar to contextual fear conditioning (Power and McGaugh 2002; Kim and Jung 2006). On this topic, it may be of interest to underline the different effects of NBM unilateral inactivation in the two paradigms. In passive avoidance, one unilateral NBM blockade was followed by amnesia (Ambrogi Lorenzini et al. 1994). In the presently reported experiments, unilateral NBM inactivation failed to impair memorization. It may be inferred that during consolidation fear conditioning does not need the simultaneous integrity of both hemispheres to be memorized.

Thus, previous and present findings clearly support an important NBM role in aversive conditioning consolidation. It must be recalled that NBM bilateral irreversible lesions due to 192 IgG-saporin administration performed in pre-acquisition (Conner et al. 2003; Frick et al. 2004; Knox and Bernston 2006) and post-acquisition (Frick et al. 2004) were not followed by significant acquisition and retention of fear conditioning impairments, either to discrete CS (Conner et al. 2003; Frick et al. 2004; Knox and Bernston 2006) or to context (Frick et al. 2004). This difference in findings may be explained by the different techniques employed. While excitotoxin 192 IgG-saporin causes lesions se-

Figure 3. Effects of NBM bilateral TTX inactivation at increasing post-acquisition delays (0.25, 24, and 48 h) on fear conditioning to context and acoustic CS. Black columns are TTX-injected groups; white columns are saline-injected groups. Mean ± SEM freezing as percentage of total 3-min period during retention testing (performed 72 and 96 h after TTX or saline administration) in the conditioning apparatus without acoustic stimulation (context) and in the other apparatus with acoustic stimulation (CS). *P < 0.05, **P < 0.01; statistically significant differences between treated and respective control groups.

NBM role in fear conditioning consolidation

The present findings show that the NBM plays a necessary role in fear conditioning consolidation. Its functional integrity is needed for the memorization of conditioned freezing responses to both acoustic CS and context. In more detail, the NBM appears to be involved only in the earlier phases of acoustic CS response consolidation but is instead involved for longer durations in contextual response consolidation. The finding that the NBM is deeply involved in the memorization of the contextual fear conditioning component confirms previous findings, e.g., those concerning the NBM role in the consolidation of passive avoidance conditioning (Ambrogi Lorenzini et al. 1994). This paradigm is indeed thought to be sufficiently similar to contextual fear conditioning (Power and McGaugh 2002; Kim and Jung 2006). On this topic, it may be of interest to underline the different effects of NBM unilateral inactivation in the two paradigms. In passive avoidance, one unilateral NBM blockade was followed by amnesia (Ambrogi Lorenzini et al. 1994). In the presently reported experiments, unilateral NBM inactivation failed to impair memorization. It may be inferred that during consolidation fear conditioning does not need the simultaneous integrity of both hemispheres to be memorized.

Needle tips were centered on NBM. On the basis of previous reports on direct measures of inactivated nervous tissue radius after TTX administration (1–1.5 mm for 8–10 ng TTX in 0.8–1.0 µL) (Zhuravin and Bures 1991; Baldi et al. 2007), it appears possible to estimate the blockade due to the injected dosage (4 ng in 0.4 µL to be circumscribed to the NBM). Retention testing was always performed 72 and 96 h after TTX administration. Following the paradigm, the NBM was inactivated only during consolidation. There was no interference with acquisition, inactivation always being performed after the acquisition session, or with retrieval. Retention testing was always performed when there were no residual TTX effects (Zhuravin and Bures 1991). The absence of interference with normal function both during acquisition and retrieval excludes not only any state-dependent effects but also any interference with acoustic CS and US sensory perception or with motor control functions. It is useful to underline the characteristics of the presently employed experimental design. In fact, when discussing the results of investigations of the NBM role in learning and memory, it has been repeatedly asked whether the experimental manipulations exerted any interference on sensory perception and/or motor performance control (Dunnett et al. 1985; Conner et al. 2003). It is evident that the presently reported mnemonic impairment can be related only to the effects of the experimental procedures on memory processing. Moreover, the time course of the presently employed paradigm does not allow sufficient time for vicarious neural circuits to be activated.

Figure 4. Absence of generalization in rats after TTX and saline injection in the NBM. Mean ± SEM freezing as percentage of total time in the first 3-min period in the new context without acoustic CS presentation during retention testing. (For details, see Materials and Methods.)
lectively on NBM cholinergic neurons that project to the neocortex (Berger-Sweeney et al. 1994; Wrenn and Wiley 1998), TTX functional inactivation is not selective for either the NBM–cortex or the NBM–amygdala projections. Consequently, TTX inactivates both projections, while 192 IgG-saporin inactivates only one of them. Thus, NBM–cortex projection may play a lesser role in the memorization process of aversive responses. Conversely, the selective lesion of the cholinergic NBM neurons projecting to the amygdala by means of phthalic acid local administration is followed by a significant impairment in acquisition and retention of an inhibitory avoidance task. Power and McGaugh (2002) concluded that the NBM-basolateral amygdala projection is certainly involved in the memorization of avoidance responses. Therefore, it may be inferred that NBM–amygdala cholinergic projection is more important than the NBM–cortex one in the memorization of aversive emotional responses. This contention is further supported by our previous results obtained by means of the same technique. Previously reported basolateral amygdala inactivation effects on context learning appear to be similar to the present results. Conversely, basolateral amygdala inactivation is followed by a more severe mnemonic impairment of acoustic CS learning (Sacchetti et al. 1999b). Moreover, the results of TTX inactivation of the frontal and parietal cortices show that there are selective impairments of acoustic CS learning, while context learning is not negatively affected (Sacchetti et al. 2003). These findings show that acoustic CS consolidation involves both amygdala and neocortex. On the other hand, there is sufficient experimental evidence to conclude that the mnemonic elaboration of the trace taking place in these sites is not dependent on their NBM connections. In fact, as stated above (1) basolateral amygdala inactivation learning impairments are more evident than those following NBM inactivation, and (2) NBM–neocortex projection selective lesions are not followed by fear conditioning impairment (Conner et al. 2003; Frick et al. 2004; Knox and Berntson 2006). Moreover, concerning cholinergic basolateral amygdala role in fear conditioning consolidation, it was shown that post-acquisition local scopolamine injection was followed by context freezing retention impairment (Passani et al. 2001). Indeed, a more precise investigation of NBM–amygdala cholinergic innervation influence on learning and memory could be of interest. The experimental procedure could include the infusion of a cholinergic antagonist in the basolateral amygdala during NBM TTX inactivation.

It has been maintained that the mnemonic impairments measured after NBM inactivation are more the consequence of attention and arousal modifications during training than the expression of an NBM mnemonic function (Wenk 1997). Even if on the basis of the present results it is not possible to exclude totally some interfering effect of TTX administration on arousal, it is possible to exclude a selective, unique interference on arousal. First, NBM inactivation performed at 24-h post-acquisition delay is still followed by impairment of the context freezing response. Indeed, it appears to be debatable whether after such a long delay the arousal connected to acquisition training is still an active or determinant factor. Second, the use of the presently employed technique of reversible functional inactivation performed during post-acquisition ensures that NBM function will be suppressed only during consolidation and not during retention. This means that during retention there cannot be any interference with arousal, interference that instead may not be completely excluded after irreversible NBM lesions.

In conclusion, the present findings confirm the role of NBM in fear conditioning consolidation by giving a temporal dimension of its involvement in the mnemonic process. In particular, the results indicate a prevalent influence of the NBM on the basolateral amygdala in the elaboration of the contextual trace.

Materials and Methods

Animals

Seventy-day-old male albino Wistar rats (average body weight, 290 g; Morini, San Polo d’Enza, Reggio Emilia, Italy) were employed. The animals were individually housed in stainless steel cages in a room with a natural light-dark cycle and constant temperature of 20 ± 1°C. The rats had free access to food and water throughout the experiment. All animal care and experimental procedures were conducted in accordance with Italian legislation and the official regulations of the European Communities Council on use of laboratory animals (directive of November 24, 1986; 86/609/EEC).

Behavioral procedures

Apparatus

As in previous experiments, a basic Skinner box module (Modular Operant Cage, Coulbourn Instruments Inc.) was employed to induce fear conditioning (Sacchetti et al. 1999a,b). Box dimensions were 29 cm × 31 cm × 26 cm. The top and two opposite sides were made of aluminum panels. The other two sides were made of transparent plastic. The floor was made of stainless steel rods connected to a shock delivery apparatus (Grid Floor Shocker, Coulbourn Instruments Inc., Model E13-08). There was a loudspeaker to emit acoustic stimuli of known intensity, frequency, and duration. The apparatus was connected to a stimulus programming device (Scatola di comando Arco 2340, Ugo Basile) in order to predetermine number, duration, and rate of CS–US couplings. The apparatus was placed in an acoustically insulated room (3.5 [h-min] × 1.8 [h-min] × 2.1 [h-min]), kept at a constant temperature of 20 ± 1°C. Illumination inside the room was 60 lux.

Context freezing response was measured in the same apparatus that was used for conditioning. As in previous experiments, the freezing response to acoustic CS was measured in a totally different apparatus from that employed for conditioning (Sacchetti et al. 1999a,b). The apparatus was a modified shuttle box apparatus (Ugo Basile; 20 cm × 47 cm × 20 cm). The walls were made of gray opaque plastic with black vertical stripes (width, 1 cm, spaced 3 cm apart). The lid was made of transparent plastic; the floor, of black opaque plastic. There was a loudspeaker to administer acoustic stimuli to the experimental subjects in the apparatus. The apparatus was connected to a stimulus program-
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reach maximal neural inactivation. Inactivation lasted for no less
and Watson (1986; see Fig. 1). At least 20 min were necessary to
brogi Lorenzini et al. 1994) according to the method of Paxinos
lateral (L) =

Freezing duration was measured 72 and 96 h after TTX or saline
administration. To measure contextual freezing, the animals
were again placed inside the conditioning apparatus and left
there for 3 min. While they were there, neither electrical nor
acoustic stimuli were administered. After that time, they were
brought back to the home cage. The rats’ behavior was recorded
by means of a closed circuit television system. To measure acous-
tic CS freezing, the animals were placed in the other apparatus to
avoid the facilitation of acoustic CS retention due to contextual
cues (Corodimas and LeDoux 1995). Once inside the apparatus,
the animals were left undisturbed for 3 min. After this time,
during a subsequent second 3-min period, a series of seven acous-
tic stimuli was administered, identical to that used during the
conditioning session (frequency, intensity, duration, intervals
between stimuli). The rats’ behavior was recorded for the entire
6-min period by means of a closed circuit television system, after
which the animals were brought back to the home cage. Rats of
each group were divided in two subgroups (four to five animals).
As in previous experiments (Sacchetti et al. 1999a,b), one sub-
group was tested for context freezing on one day (the first) and
for CS freezing the day after (the second), whereas the other
subgroup underwent an inverse schedule (context, second day;
CS, first day). This schedule was used to ensure that exposure of
all the rats first to context and second to CS, or vice versa, would
not bias the retention of any of the two responses (Sacchetti et al.
1999a,b).

Freezing (immobility) was defined as the complete absence
of somatic motility except for respiratory movements (LeDoux et
al. 1983). Measurements were performed by means of a stop-
watch by personnel who did not know to which experimental
group each animal belonged. Total accumulated freezing time
(i.e., total seconds spent freezing during each period) was mea-
sured.

Surgery and drug administration
NBM functional inactivation was induced by the injection of 4
ng TTX (Sigma) dissolved in 0.4 µL of saline, into points with the
following stereotaxic coordinates: antero-posterior (AP) = -1.5,
lateral (L) = ± 2.8, and ventral (V) =7.2 as in previous work (Am-
brogi Lorenzini et al. 1994) according to the method of Paxinos
and Watson (1986; see Fig. 1). At least 20 min were necessary to
reach maximal neural inactivation. Inactivation lasted for no less
than 120 min, exponentially decreasing and disappearing com-
pletely within 24 h (Zhuravin and Bures 1991). TTX was injected
under general anesthesia (ketamine, 100 mg/kg, i.p.) at different
post-acquisition intervals for each group of animals. Rats were
held in the stereotaxic apparatus. The injection needle (outside
diameter, 0.3 mm), connected with a short piece of polyethylene
 tubing to a Hamilton syringe, was fixed in the electrode holder
of the stereotaxic apparatus and introduced into the target struc-
ture; 0.4 µL of the solution was injected over a 2–2 min period,
and the needle was left in place for another 1 min before it was
slowly withdrawn.

To obtain post-acquisition NBM inactivation, different
groups of animals were injected at diverse post-acquisition de-
lays. A total of 97 rats was employed. Of these, 73 were randomly
divided into six groups, and TTX (T) or saline (S) was bilaterally
injected at three different post-acquisition delays: 0.25, 24, and
48 h. Six animals were excluded due to inadequate morphologi-
cal evidence, so that 67 animals made up the following groups,
ranging between 10–13 animals each: T-0.25, S-0.25, T-24, S-24,
T-48, and S-48. The remaining 24 rats were divided into two equal
groups. The rats were unilaterally injected at 0.25 h post-acquisition de-
lay. One group received TTX (TU-0.25); the other, saline (SU-
0.25). In order to ascertain if there were right-left differences in
fear conditioning consolidation, injection was performed on the
right side in 50% of the experimental subjects and on the left in
the other 50%. Since right and left NBM unilateral inactivation
did not differentially affect fear conditioning consolidation mea-
sured during retrieval testing, all the unilaterally treated rats
were grouped together.

Statistical analysis
One-way ANOVA and mixed ANOVAs were used, with treatment
(TTX and saline) and different post-acquisition delays (for the
bilaterally injected rats) as a between-subject variable and with
context and CS freezing as a within-subject variable, as well as the
Newman–Keuls’ multiple comparisons test.

Morphology
At the end of the experiments, injected sites were histologically
verified. Rats were deeply anesthetized and intracardially per-
fused with saline, followed by 4% formaldehyde. Brains were cut
with a freezing microtome, and injection needle tracks were
identified in Nissl-stained serial sections (Fig. 1). Rats with inad-
equate histological evidence were excluded from data processing.

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