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ACTIVATION OF THE DOPAMINERGIC SYSTEM OF MEDIAL PREFRONTAL CORTEX OF GERBILS DURING FORMATION OF RELEVANT ASSOCIATIONS FOR THE AVOIDANCE STRATEGY IN THE SHUTTLE-BOX

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Contents

Abstract

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1. A detailed analysis of behavior is a prerequisite for identification of components of information processing during learning.
2. Components of shuttle-box learning like the signal detection and signal evaluation can be differentiated using behavioral events such as the attention response and the orienting response.
3. Chiefly during evaluation of signal meaning in the acquisition phase of the avoidance strategy the extracellular DA is increased in mPFC.
4. The kinetics of prefrontal dopaminergic activation from trial to trial depends on the stage of avoidance learning.
5. The increase of DA in mPFC can be an indicator for the involvement of working memory principles in signal evaluation stages of conditioning.

Keywords: attention response, avoidance strategy, dopamine, gerbil, in vivo microdialysis, orienting response, prefrontal cortex, shuttle-box, working memory.

Abbreviations: attention response (AR), conditioned response (CR), conditioned stimulus (CS), dopamine (DA), constant high performance (CHIP), high performance liquid chromatography (HPLC), low increase of performance (LIP), medial prefrontal cortex (mPFC), orienting response (OR), reaction time (RT), strong improvement of performance (SIP), tetrodotoxine (TTX), unconditioned stimulus (US).

1. Introduction

The authors are interested in correlations between the activities of neurotransmission systems of learning-relevant brain areas and stages of information processing during learning. Thereby it is our strategy to break down theoretical concepts of animal learning into components which can be related to highly time resolved behavioral events during a learning process. The occurrence of these behavioral events may in turn be related to dynamics of transmitter system activations.

In the avoidance learning model "shuttle-box" gerbils (*Meriones unguiculatus*) initially respond to the unconditioned stimulus electrical footshock (US) by an escape to the other shuttle-box compartment. During training the gerbils adapt to a complete tone-footshock-shuttle-box context by avoiding the footshock. Thereafter, the animals have developed a reliable avoidance strategy of changing the shuttle-box compartment already after onset of the tone.

The acoustic shuttle-box learning implies initially the formation of the simple primary association, namely that a formerly neutral indifferent tone takes on the general meaning to announce the footshock (signal detection). Thus, the content of this new CS meaning of the tone is initially most simple. By further information processing during training this content will be developed trial by trial to a more context-adequate meaning (Rescorla and Wagner, 1972; Rescorla, 1988) by associating the temporal relationship (Barnet et al., 1991; Barnet and Miller, 1996; Davis et al., 1989) of the shuttle-box cue stimuli tone and footshock. This is called signal evaluation (Bischof et al., 2000). For secure learning of this temporal relationship to the degree at which the animal is managing the transfer from the escape to the avoidance response, the ongoing feedback experiences from trial to trial are necessary. This implies another type of information processing, namely to store the integrated experience of the past trials with the option to compare the result with the partial experience of the actual training trial. This will influence and successively optimize the decision for the action during the next trials. It is hypothesized that the properties of the so-called working memory fulfill the functions of short term storage of information and their context-adequate comparison with the consequence of decision making in this associative learning process (Atkinson and Shiffrin, 1968; Baddeley, 1992; Baddeley, 1996). The working memory preserves a limited information in a limited time for information processing. We believe that during acquisition of a behavioral strategy in the shuttle-box the working memory is used to accumulate the partial experiences from trial to trial to shape a more and more adequate behavioral strategy (Rescorla and Wagner, 1972). We obtained evidences that the hypothesized stages of formation of the avoidance strategy exist and that there is a connection to known neurotransmission mechanisms of working memory.

Specifically, we found correlations between the kinetics of the dopaminergic transmission system, measured by microdialysis from the mPFC and HPLC analysis on the one side and video-based behavioral data during shuttle-box learning on the other side (Stark et al., 1999).

2. A Detailed Analysis of Behavior During Acquisition of an Avoidance Strategy

2.1. Videobased Behavioral Analysis for Determination of Components of Information Processing During the Learning

For the behavioral test the authors used a modified computer-controlled shuttle-box (Coulbourn Instruments) within an isolation cubicle. A sinusoidally frequency-modulated tone (0.9 - 10 kHz, 2.0 Hz modulation frequency, 60 dB SPL, maximum duration 20 s) was used as an auditory conditioned stimulus (CS). 5 s after the onset tone was followed by a footshock (0.6 mA pulses, maximum duration 15 s, scrambled via a grid floor). Tone and shock were disrupted when the gerbil had changed the compartment. In this standard avoidance paradigm a compartment change within 5 s after CS-onset was rated as a conditioned response (CR) in terms of footshock avoidance.

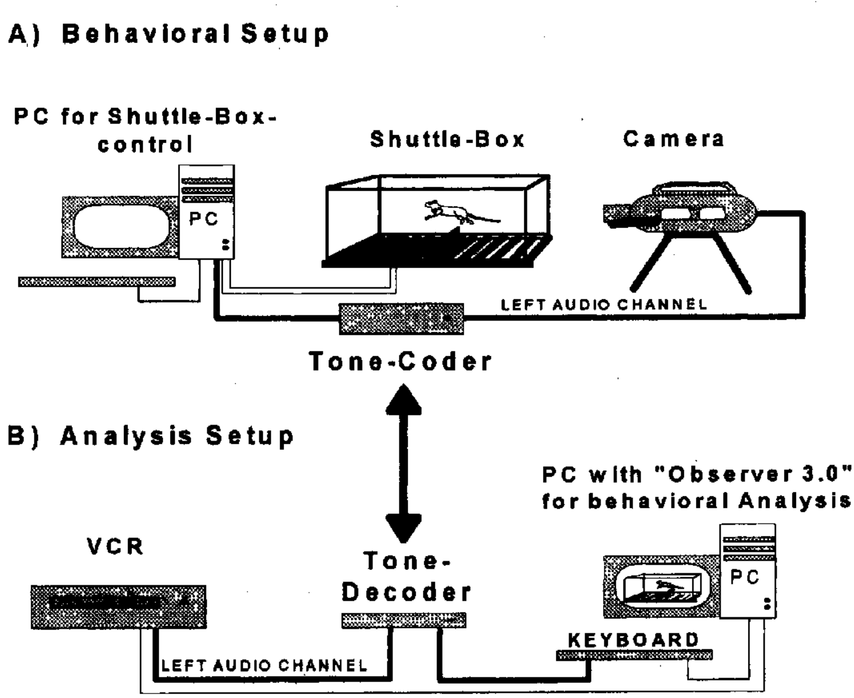

Fig. 1. Setup for behavioral measurements and behavioral analysis of shuttle-box training.

The behavior of male gerbils weighing 80-100 g in an age of 9 to 12 months during training sessions was recorded by a CAM-corder (Panasonic DP 200) using an integrated video internal time coding (VITC). Signal impulses of the shuttle-box controlling PC were later used for behavioral analysis. Impulses were transformed into tone frequencies of the DTMF (Dial Tone Multi Frequency)-code for dialing phone numbers and inserted in the sound track of the video tape. After the behavioral test the video tape was monitored for key behavioral events during training. Each defined behavioral event, e.g. an attention response (AR), obtained a key and time code, which were stored in a PC in the observational data-file (ODF) (Noldus, 1991) of the test animal (Fig. 1). The DTMF coded tones of the trigger impulses on the video tape are decoded by a DTMF-decoder and their occurrence was also stored in the ODF. After transforming this ODF into an Excel-file (Microsoft Excel 5.0®), custom-made Excel-macros assembled the time-coded data of behavioral events for different analyses (Fig. 2).

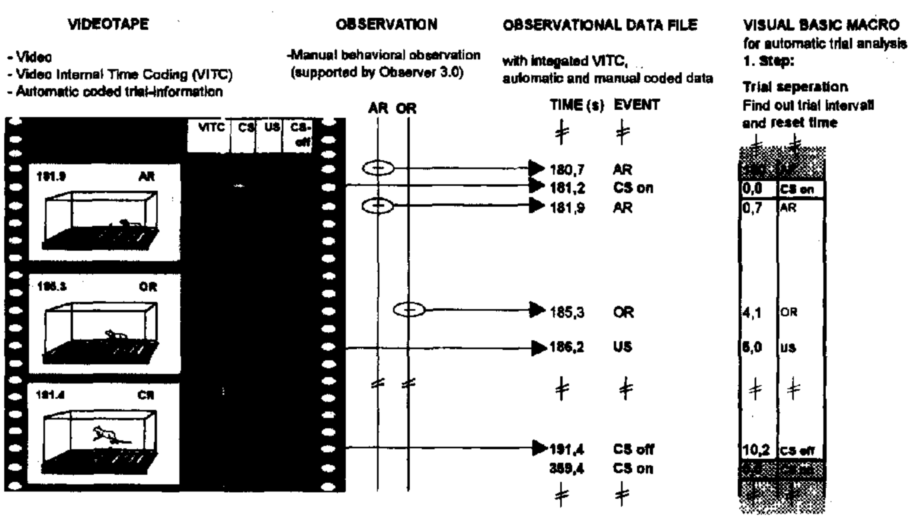

Fig. 2. Principle for time coding of PC-controlled triggers of shuttle-box training paradigm and time-coded visual analysis of behavioral events in an observational data file (ODF). After transfer of the ODF into an Excel file the single trials during shuttle-box learning were separated and automatically analyzed by Excel visual basic macros for the different behavioral events during shuttle-box training.

2.2 The Differentiation of Signal Detection and Signal Evaluation as Components of Information Processing During the Learning in Comparison With the Retrieval of the Avoidance Strategy

As conventionally done, the authors measured avoidance performance in percent of conditioned responses within 5 trials (CR%) and the reaction time (RT) as the interval from CS-onset to change of compartment in order to monitor the acquisition of avoidance behavior in the shuttle-box. In addition to these parameters we introduced the attention response (AR) and the orienting response (OR) for a more detailed analysis of the behavioral strategies.

We defined a short movement arrest of ongoing behavior after onset of CS tone as an attention response (AR). We interprete the ARs as a sign of specific information processing in this way that the formerly neutral stimulus tone will be identified as a relevant signal CS (signal detection).

The first orienting response (OR_1) in terms of an orientation of the animal toward the hurdle was considered as a sign of initiation of a motor response, but not of the final execution of the motor response itself. We interprete this behavioral event as an indicator of the association concerning the temporal relationship of the cue stimuli CS and US.

At the beginning of shuttle-box training the animal showed the signal detection as the first stage of the avoidance strategy formation. The tone was now associated with the footshock, but still not fully defined. The frequency of the first of these events (AR_1) was strongly increasing over the trials in control to the OR_1. This stage of signal detection is characterized by a Low Improvement of Performance (LIP).

During the next stage of signal evaluation the animals were forming the avoidance strategy by processing the temporal relationship between CS-onset and US-onset. The AR_1 was always present immediately after CS-onset. At the beginning of shuttle-box learning the OR_1 was sporadically observed immediately after US-onset. During the course of training the OR_1 will move more and more toward the CS-onset before US-onset. This occurs presumably as a result of an internally guided cognitive process. Furthermore, the RT was shortened close to the 5 s limit of US-onset up to the moment when the first CR occurred by further shortening of the RTs. The avoidance strategy was optimized by the gerbil from trial to trial and thereby presumably encoded as CS meaning or CS content (Bischof et al., 2000). This stage of shuttle-box learning is characterized by a Strong Improvement of Performance (SIP).

After stabilization of the avoidance strategy formation, the rank order of behavioral events immediately after CS-onset was AR_1, OR_1, and the CR before the US-onset. Now the animal retrieved the acquired avoidance strategy from memory. In this stage of the retrieval of the avoidance strategy a Constant HIgh Performance (CHIP) was found.

3. Increase of Extracellular DA in mPFC of Gerbils During Acquisition of the Avoidance Strategy

3.1. Post Hoc Definition of Behavioral Stages of Individuals During Shuttle-Box Learning and Correlation with Extracellular DA Using Microdialysis from Right mPFC and HPLC Analysis

It was previously shown that in auditory cortex of gerbils, the DA transmission system is strongly activated during auditory avoidance conditioning in a shuttle-box (Stark and Scheich, 1997). This raises the question whether more dense termination areas of DA system, for instance the learning relevant mPFC, are likewise involved in this type of avoidance learning. So far, it is known that the DA transmission in the mPFC of primates plays an important role in cognitive functions (Berman and Weinberger, 1990; Goldman-Rakic, 1992). For instance, working memory is impaired by DA depletion in mPFC (Brozoski et al., 1979; Sawaguchi and Goldman-Rakic, 1991; Sokolowski et al., 1994) and impaired working memory can be improved by DA agonists (Arnsten et al., 1994).

In the present study microdialysis technique in mPFC was used in combination with the described behavioral measures. Thereby, individual learning progress could be monitored and related to DA levels.

Six male gerbils were stereotaxically implanted (A-P 2 mm, M-L 0.8 mm, D-V 2.7 mm) under anesthesia with a microdialysis probe (CMA 12, 2 mm; Sweden) into the right mPFC. 26 and 50 h after implantation animals performed a first and a second training session with a combination of tone (CS) and footshock (US). After the experiments the probe position was histologically verified.

During behavioral experiments in the shuttle-box, the probe in mPFC of animals was perfused with Ringer. Three sequential 10 min-samples immediately before stimulation were obtained for calculation of individual base level of measured DA set to 100 %. During the stimulation period with 30 trials, six fractions and after stimulation one fraction were collected (methods see Stark et al., 1999).

The following behavioral parameters were obtained from the video recording of animal performance: (1) the avoidance performance CR, (2) reaction time RT, (3) the first attention response AR_1, and (4) the first orienting response OR_1. As a result of characteristic combinations of the behavioral parameters (1), (2), (3), and (4) during each training session, the performance of the six animals was post hoc divided into three stages: (i) Low Improvement of Performance (LIP, 2 of 6 animals during the first training session); (ii) Strong Improvement of Performance (SIP, 4 of 6 cases during the first and 2 of 6 cases in the second training session); (iii) Constant HIgh Performance (CHIP, 4 of 6 cases in the second training session). Data from these performance stages in animals were recombined as group data for analysis (Stark et al., 1999).

The occurrence during a session of CR, AR_1, and OR_1 after CS-onset was expressed in percent. Data were calculated as mean of 5 trials each. The RTs were averaged over five trials. DA levels in dialysates were expressed as percentages of basal values in each animal and each training session. The temporal profiles of CR-performances and of the DA levels of the SIP and CHIP stages were tested for differences by MANOVA with repeated measurements. The observed levels of significance are presented in Fig. 3. LIP profiles were also different from SIP profiles but the small sample was not considered reliable enough for statistics. The tests for differences between means of corresponding DA-fractions at different performance stages were performed with the Newman-Keuls test.

The following results were obtained:

(i) LIP (n = 2): In the LIP phase there was a steep increase of ARs up to 100 % from initially low levels. The increase of CRs from zero level to less than 20 % was slow and accompanied by a shortening of the RT to the footshock with only rare avoidance of the shock. The likelihood of AR_1 appearance increased over the trials of this session. In comparison the appearance of OR_1 was inconsistent. This suggests that the CS became a meaningful stimulus, but that the CS dependent avoidance strategy was undeveloped (Fig. 3 A,B,C,D). There was no increased activity of the dopaminergic system at this stage (Fig. 3 E).

(ii) SIP (n = 6): The percentage of ARs was already higher than 75 % at the beginning of training and was further increased to 100 %. The OR_1 appearance starting at 50 % was irregular, but increased to nearly 100 % at the end of the session. Thus, we concluded that the gerbils took into account the temporal relation of onsets of CS and US stimuli. Starting approximately from trial 10, the RTs were shortened into a critical range around 5 s, i.e. the jumping occurred frequently before US presentation leading to footshock avoidance. Animals at this stage in comparison to the LIP stage showed a stronger increase in performance from initially 13 % to 47 % at the end of sessions. This increase is presumably related to the formation of the avoidance strategy. This could be derived from the stable high avoidance which resulted on the next day in these four cases (Fig. 3 A,B,C,D). During this SIP stage extracellular DA level steadily and significantly increased until the middle of the training session and dropped before the session was terminated (Fig. 3 E).

(iii) CHIP (n = 4): Animals showed the AR_1 and OR_1 to 100 % and the avoidance response CR at a stable level of more than 60 %. The means of RTs of these animals decreased shortly after initiation of the training session below the 5 s-limit, i.e. the established strategy was already transferred to the CS (Fig. 3 A,B,C,D). The CHIP stage therefore mainly involves recall of the learned strategy. DA levels were not increased during this stage (Fig. 3 E).

The comparison of the time course of behavioral measures with those of the relative DA values at the LIP, SIP, and CHIP stage revealed that only during the strongest improvement of performance during the SIP stage, i.e. during acquisition of the avoidance strategy, there was initially a strong increase of extracellular DA in mPFC which was followed by a decrease. The DA profiles of the CHIP stage were significantly different from SIP profiles (MANOVA $p < 0.05$) (Fig. 3 D,E).

The present investigations revealed a significant difference in extracellular DA between the acquisition and the retrieval of a shuttle-box avoidance strategy in mPFC of gerbils. The DA system of the mPFC in primates is strongly involved in cognitive functions tested by working memory tasks (Goldman-Rakic, 1992; Schultz, 1992; Watanabe et al., 1997). The working memory based on short-

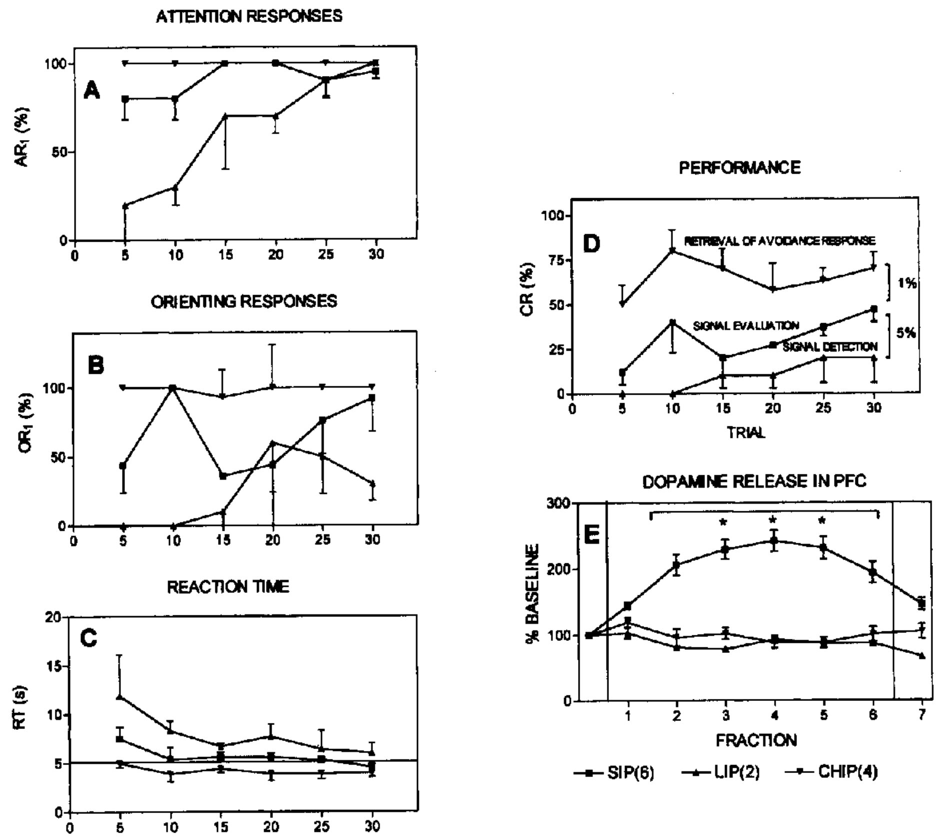

Fig. 3. Averaged first attention response (AR_1) profiles (A), first orienting response (OR_1) profiles (B), reaction time (RT) profiles (C), and performance profiles (conditioned responses CR) (D) of animals groups during stages of Low Improvement of Performance (LIP), of Strong Improvement of Performance (SIP), and of Constant HIgh Performance (CHIP). A data point is the mean of 5 trials of all animals of a group ± SEM. In the CR% analysis solid brackets indicate significant differences found within the stimulation period between the groups of stages (MANOVA). Temporal profiles of relative content of DA in brain dialysates during corresponding LIP, SIP, and CHIP stages of animals (E). Data are mean ± SEM. Profiles represent 10 min-samples including 5 trials each during the stimulation period (between vertical lines). DA values are related to the average of the three 10 min-samples before stimulation defined as 100 % base level. The first 6 values represent the stimulation period and the last value the unstimulated recovery period. In the DA analysis the solid bracket indicates significant differences between SIP stage and the CHIP stage (MANOVA, $p < 0.05$) found within the stimulation period. Significant differences between corresponding fractions of SIP and CHIP stage are indicated by asterisks (Newman-Keuls-Test, $p < 0.05$)

term storage is vulnerable to DA loss (Goldman-Rakic, 1992). The hypothesis of working memory implies that a foregoing cognitive information is temporarily kept in such a way that it can be related to following input of information (Atkinson and Shiffrin, 1968; Baddeley, 1992; Baddeley, 1993; Baddeley 1996). It is assumed that this system is used for the performance of many cognitively demanding processes involved in comprehension and problem solving (Eysenck et al., 1997). Obviously, in the SIP stage of avoidance learning animals associated the most important temporal relation of the cue stimuli CS tone and US electric footshock for the formation of the shuttle-box avoidance strategy, i.e. they learned to avoid the US-punishment by changing the compartment within the period between CS-onset and US-onset (Rescorla, 1968; Fuster, 1989).

We assume that during this acquisition stage of avoidance, the previously accumulated experience is repeatedly compared and combined with continuing feedback experiences of positive or negative trials (CR = avoidance or non-CR with punishment = escape) (Sternberg, 1969) leading to "memory-guided performance" (Goldman-Rakic, 1992). Therefore, we assume that during the SIP phase short-term storage and information processing could be utilized similar to those in working memory (Atkinson and Shiffrin, 1968; Baddeley, 1992; Baddeley, 1993; Baddeley 1996; Eysenck et al., 1997). An increase of extracellular DA in mPFC was previously found during strategy formation in an operant discrimination task (Yamamura et al., 1994; Izaki et al., 1998). In the light of the present results this may serve as a further indicator of the involvement of working memory principles in certain stages of conditioning.

In contrast, during the retrieval of the established shuttle-box avoidance strategy the dopaminergic system was not activated (Stark et al., 1999) and therefore working memory principles are presumably not required. In support of this assumption it was previously shown by Watanabe et al. (1997) in monkey mPFC that DA levels increased during a working memory task and not during a sensory-guided reference memory control task. Therefore, conscious reproduction of events and facts for comparison and subsequent decision making is driving working memory mechanisms in mPFC, whereas the retrieval of learned procedures from the memory, elicited by a external conditioned stimulus, does not require these mechanisms.

Furthermore, the present results indicate that during the initial LIP stage characterized by the presumably simple process of associating the tone with the meaning of footshock punishment, i.e. to detect the tone as a possible announcer of the footshock, working memory mechanisms may not be involved because extracellular DA was not increased.

In conclusion we hypothesize that, if during learning feedback-principles are required, working memory mechanisms are necessary for comparison and association of events and facts in order to determine their temporal and causal relationships within the context or environment (Rescorla, 1988; Baddeley, 1993; Eysenck et al., 1997). Calculating of relations (associations at a higher cognitive level) according to the working memory model of Baddeley (1992, 1993, 1996) is in the responsibility of so-called central executive.

It has been proposed that the activity of dopaminergic system is increased only by appetitive stimuli (Hernandez and Hoebel, 1990; Schultz, 1992; Feenstra and Botterblom, 1996). This is not in contradiction to our present results, since the success of avoiding an aversive reinforcement by feedback experience, i.e. the strategy finding with the help of working memory principles in mPFC could be reflected by the animals as a "reward" similar to an appetitive stimulus (Koob, 1992; Young, 1993; Salamone, 1994).

3.2. Individual Correlation of Extracellular DA from Trial to Trial During Different Stages of Shuttle-Box Learning

The aim of a further experiment was to obtain a higher time resolution in the correlation between the DA content in dialysates and individual behavior. Thereby we were able to collect dialysates from the right mPFC during the avoidance training session over 30 trials from trial to trial within 2 min intervals.

The two requirements for this experiment are a fast learning gerbil which acquires the avoidance strategy within the first training session and a sufficient DA content in the 2 min-dialysate fractions. The reliable DA detection limit for the used HPLC-analysis was 0.1 fMol per 2.8 µl sample (methods see Stark et al., 1999). For validation of DA analysis we tested in an exemplary fashion the effects of perfusions with 1 µM DA uptake blocker nomifensine (Fig. 4A) or 3 µM sodium channel blocker TTX (Fig. 4B), respectively. Similar to previous work we assumed that changes in measured extracellular DA reflect the neuronal release of DA in mPFC in response to different cognitive stages (Feenstra and Botterblom, 1996).

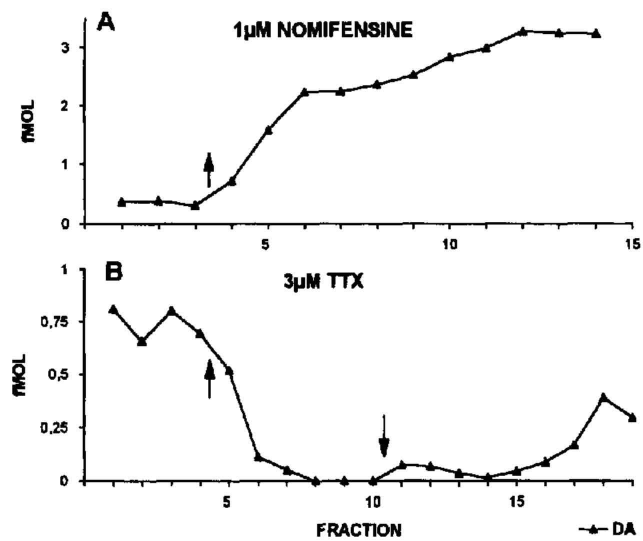

Fig. 4. The effects of perfusions with 1 μM nomifensine (A) or 3 μM TTX (B), respectively, on extracellular DA in mPFC. The upward directed arrows point to the first samples in which the substances were present (A, B). The downward directed arrow indicates the first fraction without TTX perfusion (B).

Due to the very fast learning the different performance stages are compressed and merged into one another. Nevertheless the following distinctions can be made. From the beginning to about trial 9 of the training session (defined as LIP stage) the RTs were shortened, the AR_1 were present but not yet reliably related to CS-onset. CRs were not occurring. Thereby DA content did not reach the maximum during this initial stage of learning. During the SIP stage the AR_1 occurred shortly after the CS-onset and distinct OR_1 were measurable from trial 16. At the end of this stage until trial 24 the frequency of CRs was already high. The DA content of dialysates further increased and reached its maximum at the end of this SIP stage. We assume that approximately by trial 24 the gerbil had acquired the behavioral strategy and thereafter was able to retrieve avoidance behavior. The AR_1 was closely connected to the CS-onset. In this case the OR_1 could not always be differentiated from the movement of the animal. For four trials this gerbil received an US, and the movement during compartment change was so fast, that the OR_1 was burried. We assume that the gerbil mastered the avoidance strategy in principle especially in view of the beginning decrease of the DA content in dialysates (Fig. 5A and 5B).

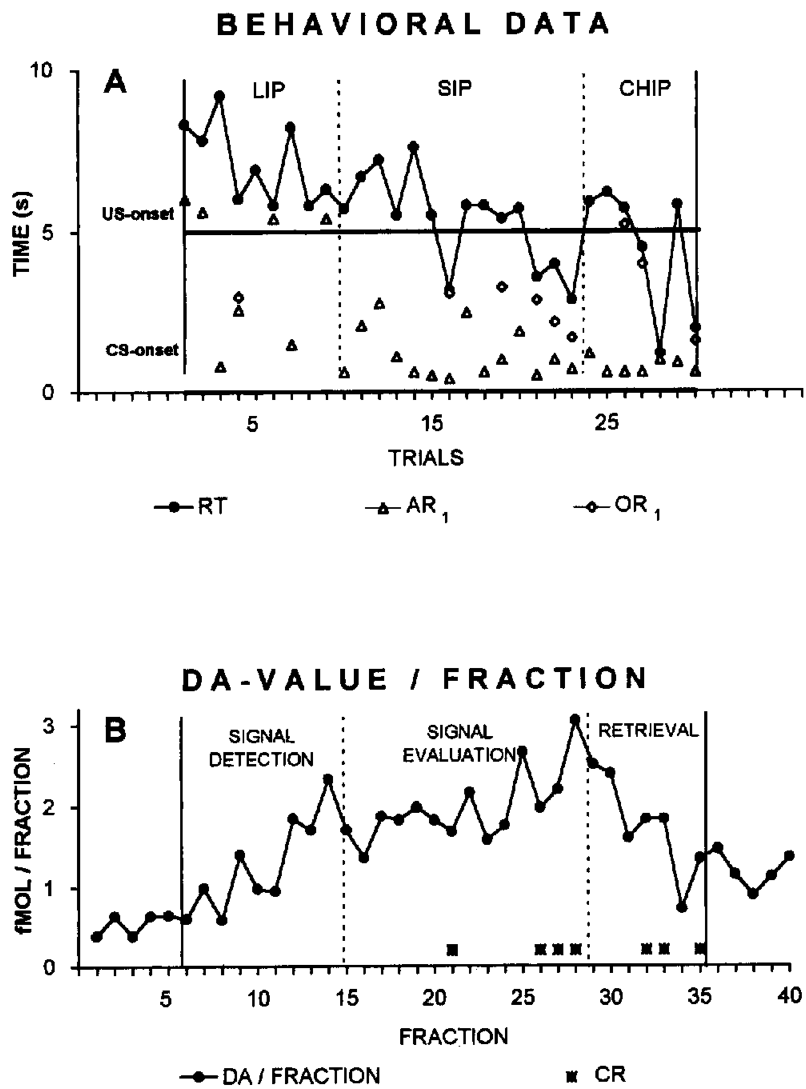

Fig. 5. Individual learning with all stages during one session: Profiles of reaction time (RT), of the first attention response (AR_1), and of the first orienting response (OR_1) versus time from CS-onset of an animal during LIP, SIP, and CHIP-stages (A). Temporal profile of DA content in brain dialysates during corresponding stages of signal detection, signal evaluation, and retrieval of the avoidance strategy (B). This profile represents 2 min-samples for each trial of the stimulation period (between vertical full lines). The first five samples and the last five samples represent DA values before and after the stimulation period.

The gerbil in the described experiment showed the signal detection, the signal evaluation, and the retrieval of the behavioral strategy all within one training session. Thereby it could be demonstrated that the key phase of shuttle-box learning, i.e. the cognition of temporal relation of onsets of CS tone and the US, is accompanied by the strongest DA increase in mPFC.

4. Conclusions

1. Signal detection and signal evaluation can be differentiated by several behavioral events during shuttle-box learning. They represent different types of associations.

2. The optimization of the specific association leading to a correct internal reflection of the temporal relationship of the cue stimuli CS tone and US footshock to avoid the US (cognition) is achieved by permanent feedback from trial to trial.

3. This feedback implies a comparison of a stored and integrated experience of the performed trials with the partial experience of the actual trial as a basis for an optimized action of the next trial.

4. The generally assumed properties of working memory are relevant for this proposed feedback and comparison of successive partial experiences during shuttle-box learning.

5. The increase of the activity of dopaminergic system in mPFC matches the acquisition phase of the avoidance strategy and is therefore an indicator of the involvement of working memory principles.

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