Effect of Amphetamine on Ventral Tegmental Area Neurons in Awake Rats

Charlotte Delairesse, Vincent Seutin [1],Stanislav Koulchitsky[1]
Neurophysiology laboratory, GIGA Neurosciences, University of Liège

[1] These authors participated equally to the work.

INTRODUCTION

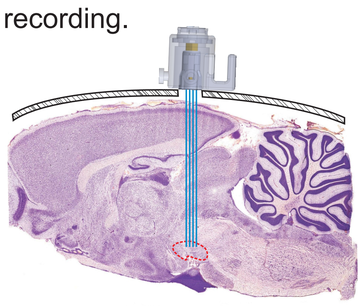
Amphetamine (AMPH) is an addictive drug targeting the dopamine (DA) system. However, its effect on the excitability of DA neurons is still unclear. In this study, we decided to investigate the firing rate of DA neurons from the ventral tegmental area (VTA), a key structure in the reward circuit and in the development of addiction, of awake rats.

METHODS

Adult male Wistar rats (n = 15) were implanted with wireless neural probes (ATLAS Neuroengineering, Belgium). Rats were then allowed 5 days to recover and thereafter entered the recording procedure (see figure 1). Electrophysiological signals and behavior were recorded simultanuously using a W16 system, Multi Channel Systems GmbH, Reutlingen, Germany and EthoVision (version 11.5,Noldus Information Technology, Wageningen,The Netherlands), respectively. Spike analysis was performed using Spike 2 V6.0 (Cambridge Electronic Design, Cambridge, UK) and MATLAB FieldTrip toolbox (Oostenveld et al, 2011). DA neurons were identified with usual criteria. Histological controls confirmed the site of recording.

A

TIME	Session A	Session B
30 mins	Baseline	Baseline
1 hour	Saline	AMPH (2 mg/kg i.p.)
30 mins	Quinpirole (0.1 mg/kg i.p.)	Quinpirole (0.1 mg/kg i.p.)



B

TIME	Session
15 min	Saline (0.5 ml, i.p.)
15 min	+ objects
15 min	AMPH (2 mg/kg i.p.)
15 min	+ objects
15 min	Quinpirole (0.1 mg/kg i.p.)

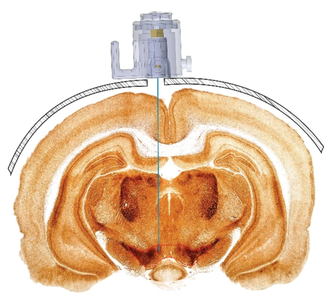


Table 1: A Recording procedure for the « behavior vs firing ». Each rats underwent the 2 sessions in a random order. **B** Recording protocole for the « object investigation » experiments
Figure 1: Schemes of implantation of the electrodes within the VTA on a sagital slice (**A**) and a coronal slice (**B**). The area surrounded in red correspond to the VTA.

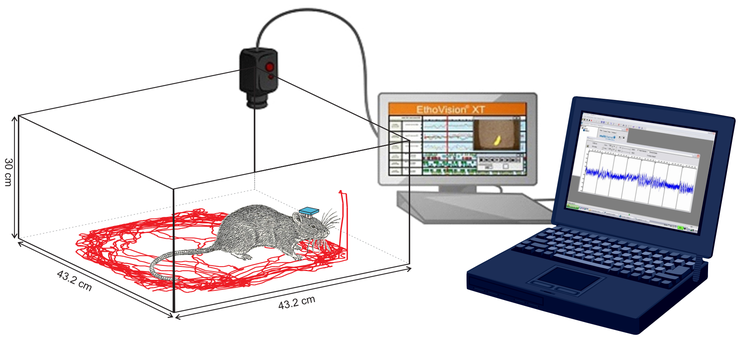
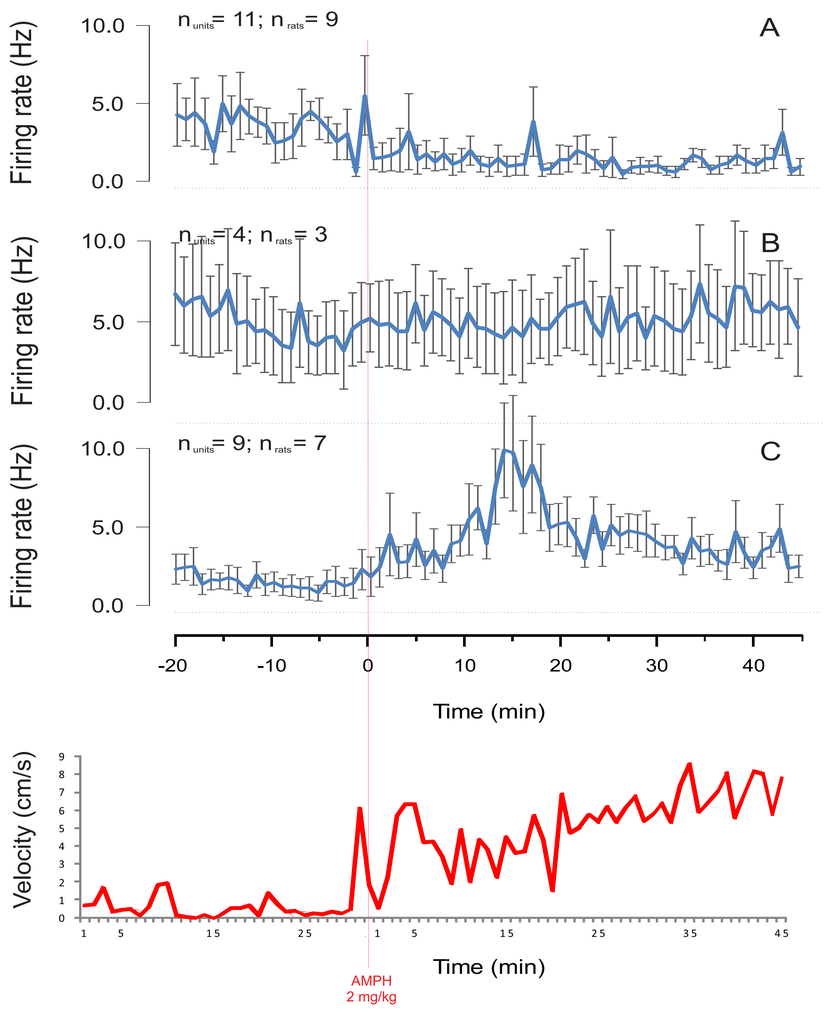


Figure 2: Recording set-up The rat is recorded in a plexiglas arena. A camera linked to EthoVision asses its locomotor behavior. Simultanuously, the electrophysiological data are sent to another computer. In red, we can see the tracking of the rat.

RESULTS



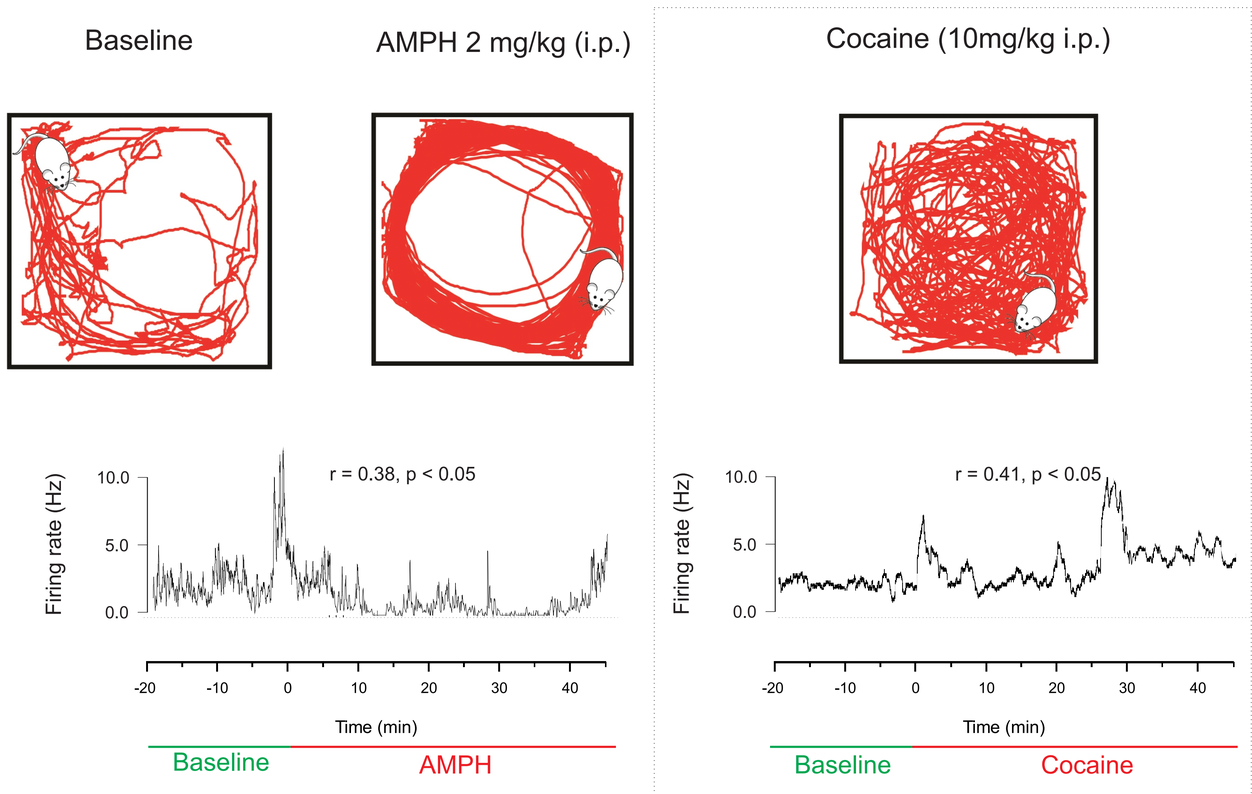
We observed various responses to AMPH in VTA putative DA neurons. We were able to classify them in 3 groups:

Group A contains DA neurons whose firing decreased after injection of AMPH. Note the parallelism between the electrophysiological data and the behavior.

Group B did not react to AMPH.

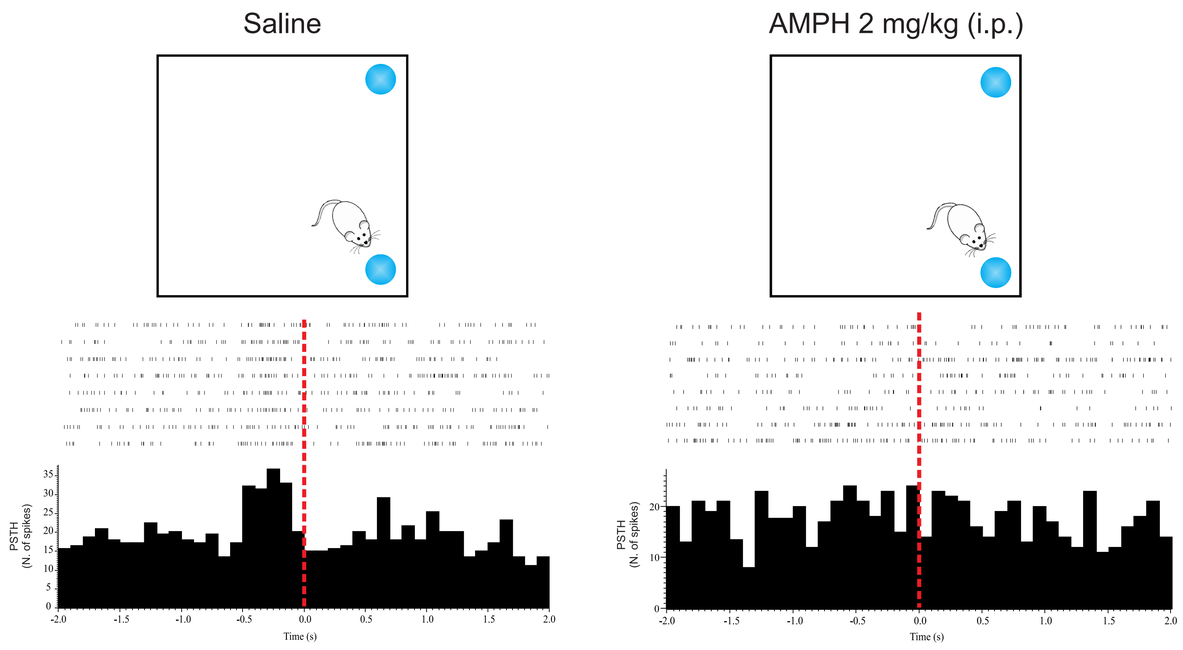
Group C shows an increase of the firing rate that is significant from the cluster « 20 mins » (p=0.032) until the « 25 mins » one (p=0.033).

Behavior vs firing



Koulchitsky *et al.*, 2012

Object investigation



Peri-event histograms. In saline-treated rats, each exploratory action was preceded by a short-term increase of midbrain DA activity. In amphetamine-treated animals, this increase was not seen.

CONCLUSION

Overall, as compare to cocaine, AMPH inhibits the firing rate of a larger population of VTA DA neurons. In parallel, the features of the locomotor activation were different with much more stereotypy for AMPH. Thus, our results support the suggestion that dissociation between post-synaptic dopamine receptor activation and pre-synaptic DA activity represent a key phenomenon leading to the development of behavioral stereotypy (Kuczenski, 1983).

Suppression of those midbrain neurons, which are directly involved in goal-directed exploratory behavior, and simultaneous passive release of the dopamine from terminals might predispose the perseverative quality of the behavioral response to amphetamine and some other dopamine-releasing agents.

This may also have direct relation to such behavioral disabilities as severe drug addiction, obsessive-compulsive disorder and Tourette syndrome, for which compulsive behavior and stereotypy are among major presenting features.

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