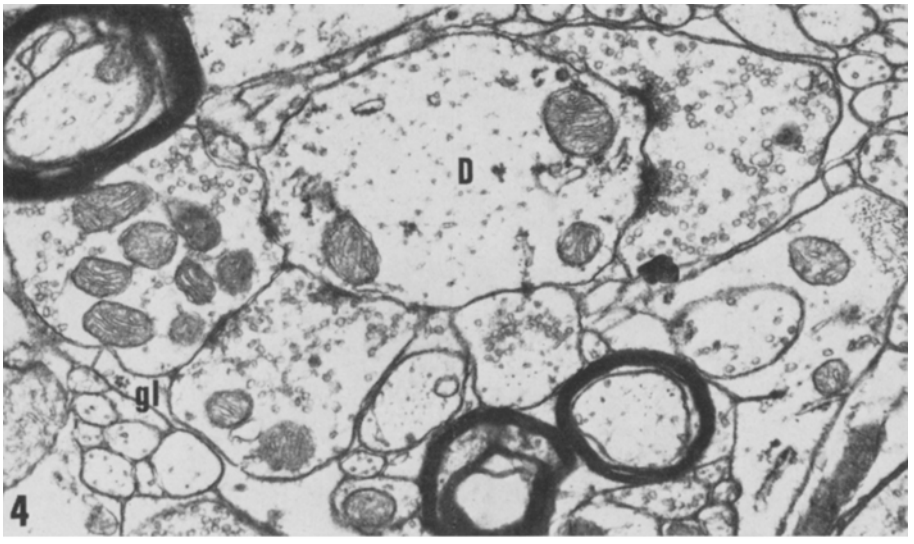

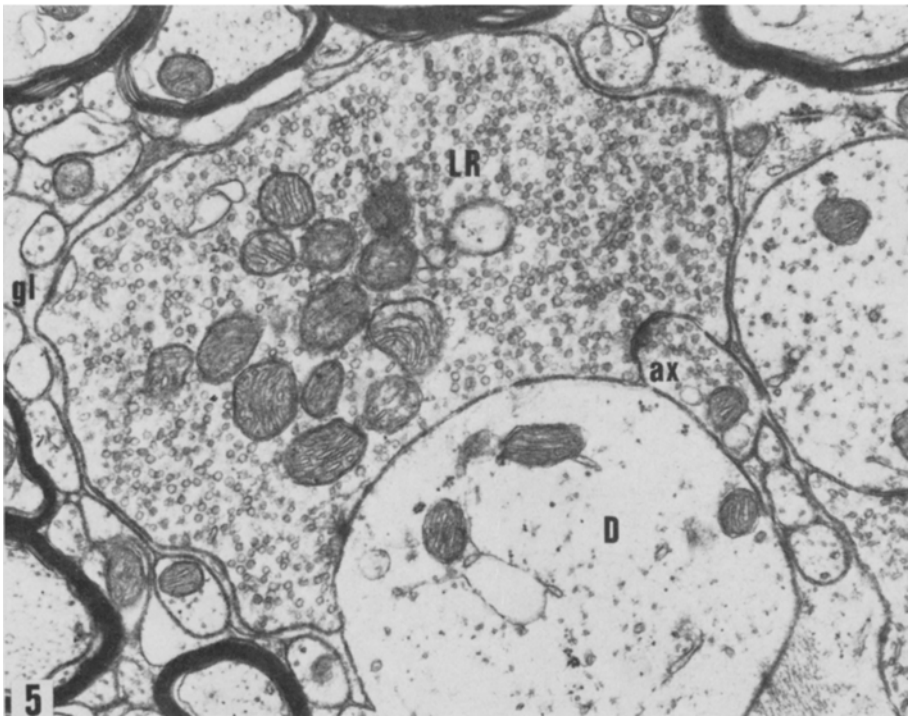

Fig. 4. A synaptic glomerulus in which a dendritic shaft (D) is contacted by small and medium sized boutons. The synaptic glomerulus is enclosed by a glial lamina (gl). ×27,500.
Fig. 5. A synaptic glomerulus in which an LR bouton makes contact with a large dendrite (D) and itself is contacted by a small axonal terminal (ax). The synaptic glomerulus is enclosed by a glial lamina (gl). ×27,500.

important mechanism by which negative feedback processes may operate in the ILN of rat.

Résumé. On a constaté que le neuroptile du noyau intermédio-latéral du rat contient de nombreux glomérules synaptiques gliaux encapsulés dans lesquels se trouve habituellement un dentrite ou axe terminal très visible surmonté par de petits boutons et des dentrites. Les glomérules sont accompagnés de synapses axo-axonaux qui peuvent être le corrolaire structural d'une inhibition présynaptique. La signification fonctionnelle des glomérules et des synapses axo-axonaux est discutée.

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Evidence for the Stimulant and Depressant Central Effects of L-α-Acetyl Methadol[1,2]

Most neurotropic drugs are thought to be either stimulants or depressants. Experimentally such a system of classification is justified on the basis of gross behavioral effects exerted by the drugs in question. Their responses represent for the most part an algebraic sum of the individual effects exerted by the drugs on the central nervous system (CNS) over a given period of time to which a subject is exposed to the drugs. Opiates and opiate derivatives

have been classified as CNS depressants. DESALVA and OESTER[3] have shown that these group of drugs supress the somesthetic pathways. Clinically the drugs exhibit diversified differences in the manifestations of symptoms associated with their use. Methadone (6-dimethylamino, -4, 4-diphenyl-3-heptanone) was shown to exhibit a slow and prolonged episode of withdrawal than morphine, meperidine and codeine[4]. By the same token the methadone derivative, L-α-acetyl-methadol (LAAM) by virtue of its long lasting action[5] is now employed as an experimental drug[6,7], in the supression of pain during withdrawal and was found not to differ from methadone, the primary pharmacotherapy for narcotic withdrawal syndrome. The mechanism(s) by which these opiate substitutes supress abstinence is not known but it is probable that it is associated with additional pharmacologic properties not related to the CNS depression by these drugs. In this paper, we report for the first time that L-α-acetyl-methadol, a long lasting narcotic exerts not only a CNS depressant action but is also a stimulant drug at low therapeutic doses.

Materials and methods. a) *Visual evoked responses* (VER). Unanesthetized, male New Zealand white rabbits (2 to 3 kg) were chronically implanted with electrodes placed in the optic cortex 15 mm lateral from the midline and the posterior sensorymotor cortex (PSMC) 15 mm posterior to the sutura coronaria. Recordings were taken against a nasal bone reference electrode. A lateral ventricle cannula instituted ipsilateral to the site of the recording electrodes permitted direct intracortical administration of a saline solution of LAAM as either a 0.5 mg/kg dose or as a 1.25 mg/kg dose. 3 to 4 animals were used for each experiment and for every dose of the drug studied. In all series of experiments, controls were run with animals administered with an equivalent volume (0.1 ml) of normal saline through a corresponding route.

During each experiment, which lasted approximately 2 to 3 h or longer, the rabbit was restrained on a hammock in an isolated, sound-proof room supplied with red light illumination using a Kodak Wratten filter No. 93. To prevent movement of the animal, and to keep the eyes in a constant light path, the rabbit's head was fixed. The pupils were dilated with pretreatment using ophthalmic drops of a 2% aqueous solution of atropine sulphate. Eyelid apertures were kept constant by an artificial pupil.

A Grass PS-2 stimulator with a PST-2 red flash lamp set at intensity 16 was used to evoke the responses with 10 μsec stimuli delivered continuously once every 2 sec throughout the experiment. Monopolar recordings of the electrical activity in both the visual pathway and the optic cortex were monitored on an oscilloscope (Tektronic

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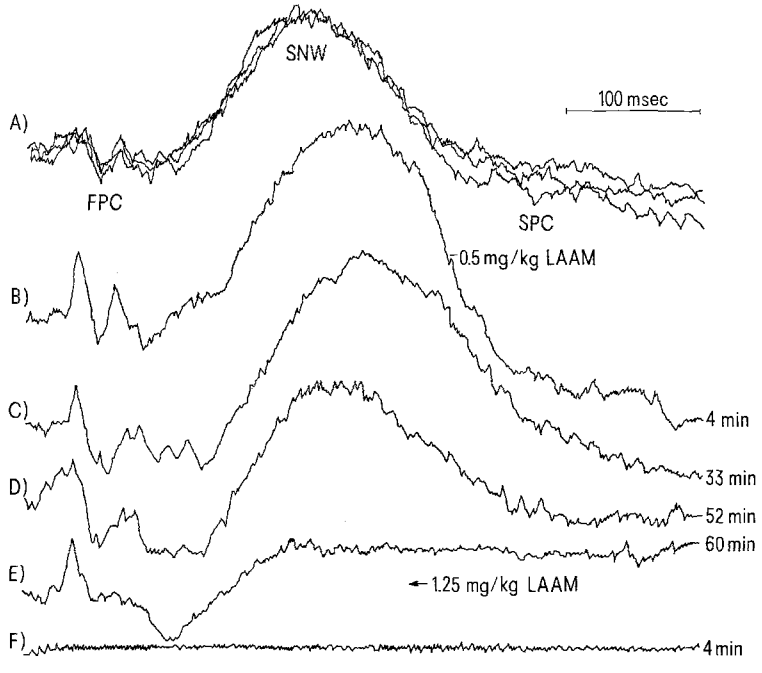

Effect of intracortical administration of L-α-acetyl methadol (LAAM) on the visual evoked responses (VER) of the rabbit optic cortex. A) controls (0.9% saline); B) C) D) and E), 4 min, 33 min, 52 min and 60 min respectively after administration of 0.5 mg/kg LAAM in 0.9% saline. Note the initial stimulant effect on the cortex 4 min post drug administration; onset of the depressant effect on the EEG was observed 60 min after drug administration. E), the EEG 4 min after administration of a 1.25 mg/kg dose of LAAM; the results represent data from a different series of experiments using different sets of rabbits; the controls were no different from A.

Effect of L-α-acetyl methadol (LAAM) on post-ictal recovery in mice following electroshock

	10 min				20 min			
Dose (mg/kg i.p.)	Latency (sec)	Pattern	Recovery (sec)	*N*	Latency (sec)	Pattern	Recovery (sec)	*N*
Saline	2.0 ± 0.13	FEC	47.7 ± 2.5	10	2.0 ± 0.12	FEC	45.1 ± 3.5	10
0.1	2.1 ± 0.14	FEC	61.7 ± 2.4	8	2.46 ± 1.1	FEC	67.3 ± 3.0	10
0.25	2.19 ± 0.11	FEC	51.8 ± 2.1	7	2.5 ± 0.16	FEC	69.3 ± 5.91	8
0.5	2.11 ± 0.11	FEC	54.3 ± 3.1	4	2.59 ± 0.22	FEC	66.9 ± 0.98	6
1.5	2.26 ± 0.14	FEC	67.1 ± 7.6	4	2.57 ± 0.16	FEC	68.3 ± 16.0	3
2.0	2.54 ± 0.11	FEC	88.8 ± 7.0	8	2.55 ± 0.13	FEC	80.9 ± 4.0	8

N, numbers of animals out of 10 surviving electroshock treatment; F, flexion; E, extension; C, clonus.

502A) after suitable amplification using a Grass P-5 amplifier. The sum of 40 VER's were analyzed during a 500 msec period by a Mnemotron 400 B Computer of Average Transients (CAT) and recorded every 2–5 min using an X-Y plotter (Mosley Model 2D-2).

Recordings were arranged so that relative negativity at the active electrode would register as an upward deflection e.g. the slow negative wave (SNW) of cortical activity whereas positivity was registered as downward deflections e.g. the fast positive complex (FPC) of the visual pathway.

b) *Electroshock Treatment.* 10 mice were used for each group of experiments and 10 for corresponding controls. Control animals were injected i.p. with 0.25 ml of 0.9% saline while experimental animals were injected i.p. with a 0.25 ml of LAAM in two different experimental groups respectively 10 min and 20 min prior to electroshock. The animals were then given electroshock by administering a D.C. current strength of 140 mV by contacting the eyes with electrical terminals. The latency period before seizure, duration of flexion, extension, and clonus were recorded in sec.

Results. a) *Effect of LAAM on the electroencephalogram.* LAAM exerted a dose-dependent biphasic effect on the EEG (Figure). An initial facilitatory effect was observed 4 min after administration of a dose of 0.5 mg/kg LAAM into the cortex. This had a duration of 52 min before the EEG normalized. However, the onset of peak amplitude of the SNW was considerably delayed (Figure B).

Thereafter a depression of the amplitude of the SNW was observed with no recorery in the delay of peak amplitude of the SNW. A dose of 1.25 mg/kg of LAAM resulted in complete abolition of the slow negative wave 4 min after intracortical administration. Recovery to control values was not obtained even after 5 h of experimentation. Administration of the drug i.v. did not alter the nature of the effects except that there was a delay in their onset.

b) *Electroshock treatment.* The post-ictal recovery of mice pretreated with LAAM in therapeutic equivalent doses before electroshock exposure, also exhibited a biphasic effect (Table). Groups of mice given electroshock either at 10 min or 20 min after drug administration had a prolonged post-ictal recovery at doses between 0.1 mg/kg and 0.25 mg/kg inclusive. This prolongation was followed by a decrease in the post-ictal recovery between the doses of 0.25 mg/kg and 0.5 mg/kg subsequently followed by a second phase of gradual prolongation of the time for doses between 0.5 mg/kg and 2 mg/kg of LAAM. A 2 mg/kg dose given to rabbits is equivalent to a dose of 140 mg/70 kg man; which exceeds the 100 mg maximum therapeutic dose permitted by the regulations of Food and Drug Administration.

Discussion. We have demonstrated in these studies that the narcotic L-α-acetyl-methadol (acute) exerts a biphasic dose-dependent effect on the rabbit cortex. These effects were qualitatively similar to but quantitatively different from the same effects reported earlier by us for methadone hydrochloride[8,9]. In those earlier experiments the stimulant action of methadone was associated with the release of tyramine and the depressant effect was attributed to either direct binding to the postsynaptic membrane or to synergism between 2-phenylethylamine and methadone.

It is probable that the same mechanism would explain the biphasic action of LAAM on the CNS especially in view of the fact that the characteristic undulating effect of LAAM on post-ictal recovery of mice had also been reported by us for methadone[9]. These latter results may serve some purpose in the elucidation of the mechanisms of dose dependent seizure induction by some narcotics either during opiate administration or during withdrawal. Furthermore, it was of interest that LAAM, as was also the case with methadone[9] did not alter the latency to seizure at neither subtherapeutic, therapeutic or above-therapeutic doses. These results are not consistent with the notion that methadone or its congeners may have antipsychotic properties. The probable clinical suppression of psychosis by these drugs at certain doses may thus be related to their sedative effects.

Zusammenfassung. Nachweis, dass L-α-Acetyl Methadol (LAAM) nicht nur zentralnervös sedierenden, sondern auch stimulierenden Effekt hat. Im Tierversuch zeigt sich bei elektroenzephalographischen Ableitungen bei visueller Stimulierung und Elektroschock-Behandlung ein 2-phasiger, von der Dosierung abhängiger Effekt des LAAM auf das Zentralnervensystem, was den Erfahrungen mit Methadon Hydrochlorid entspricht.

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