TITLE: 5α-PREGNANE-3α-OL-20-ONE IDENTIFIED AS AN ACTIVE MOLECULAR SPECIES OF STEROID ANESTHETIC IN BRAIN.

AUTHORS: N.R. Krieger,Ph.D., W.M. Mok,Ph.D., S. Herschkowitz,M.D.
AFFILIATION: Anes. Dept., Harvard Medical School, Brigham & Women's Hospital, Boston, MA 02115.

The molecular species responsible for steroid anesthesia have proved difficult to identify because numerous metabolites are formed in brain. The comparison of brain levels at different behavioral endpoints provides a strategy for the identification of the active molecular species. Two criteria were used to identify the active species. Levels of the active steroid were supposed to be lower at the return of the righting response (RRR) than at the loss of the righting response (LRR); and, in groups of mice that received different doses, levels of the active steroid were supposed to be the same at LRR.

Mice (20g; male albino CD-1) were anesthetized with 3 mg/kg i.v. [^{3}H] 5α-pregnane-3α-ol-20-one (3α) in 20% Cremaphor EL. Steroids were resolved and quantitated by TLC and liquid scintillation spectrometry. At LRR, which occurred within 6-10 sec, brain levels (mean ± SEM) for 3α and its metabolite, 5α-pregnanedione (5α), and the unidentified metabolites, ko, k1, k2 and k3 were 6.11 ± 0.66; 0.07 ± 0.05, 0.02 ± 0.02, 0.16 ± 0.09, 0.19 ± 0.05 and < 0.04 pmol/mg tissue respectively; (n = 5). At RRR, which occurred 10-22 min later, these levels were (3α) 3.63 ± 0.26, (5α) 0.23 ± 0.03, (ko) 0.82 ± 0.09, (k1) 1.15 ± 0.17, (k2) 0.76 ± 0.07, (k3) 0.13 ± 0.07 pmol/mg (n = 6). With a lower administered dose (2.5 mg/kg) LRR occurred later (1-4 min) and steroid levels were (3α) 5.46 ± 0.32, (5α) 0.17 ± 0.01, (ko) 0.36 ± 0.09, (k1) 0.51 ± 0.08, (k2) 0.30 ± 0.08, (k3) 0.12 ± 0.05 pmol/mg (n = 5). 3α levels were significantly lower at RRR than at LRR ($p < 0.0005$). While the other 5 agents were each higher at RRR than at LRR. For two different anesthetic doses, levels at LRR did not differ significantly for 3α ($p > 0.2$); 5α ($p > 0.05$) and k2 ($p > 0.2$) while levels for ko ($p < 0.01$); k1 ($p < 0.02$) and k3 ($p < 0.05$) were significantly higher with the higher dose.

Of all the steroids measured only 3α was lower at RRR than at LRR and exhibited the same levels at LRR for two different doses. 3α was judged to be responsible for the onset and maintenance of anesthetic activity.

This study was supported in part by the NIH (GM 42672).

A705

TITLE: MINIMUM ALVEOLAR CONCENTRATION OF SPINAL CORD REFLEXES IN RATS

AUTHORS: S.G. Soriano, M.D., J.L. Benthuysen, M.D., J.A. Reitan, M.D.
AFFILIATION: Department of Anesthesiology, University of California, Davis, CA 95616

Introduction: Minimum alveolar concentration (MAC) is the standard for determining the potency of inhalational anesthetics[1]. It is unclear to what extent these agents depress cortical perception or reflex responses to stimuli. The purpose of this study is to assess the MAC needed to suppress spinal cord reflexes and to compare the MAC of spinal cord segments with and without cortical input.

Methods: Approval was obtained from the Animal Research Committee. Baseline MAC values for isoflurane were obtained from eighteen 200-250 gram female rats using the rachet clamp technique on the forelimb, hindlimb and tail. Inspired isoflurane concentrations were measured by mass spectrometry (SARA). After a seven day recovery period, the rats were randomly assigned into either a sham (n=8) or spinalized group (n=10). Spinal cord lesions were produced by an electrocautery needle at T_{7-9}. After spinal reflexes were established in the spinalized group, MAC determinations were repeated on both groups. The differences in the pre- and post-treatment MAC for each group were compared for each extremity above and below the lesion by unpaired t-test. A p value < 0.05 was considered significant.

Results: The mean and SEM MAC values (%) are depicted in the following table:

	control(18)	sham(8)	spinal(10)
forelimb	1.21±.06	0.98±.05	0.95±.05
hindlimb	1.32±.07	1.12±.07	0.77±.05
tail	1.01±.07	0.80±.02	0.64±.04

The decrease in MAC below the level of the lesion in the spinalized group ($p < 0.001$) was greater than the corresponding change in the forelimb in both groups ($p = 0.002$).

Discussion: Our study demonstrates that spinal cord reflexes can be abolished with isoflurane concentrations of 0.64-0.77%. This value is considerably less than the MAC of the intact rat[2]. The unexpected reduction in the MAC of the forelimb may be attributed to generalized cachexia as well as accommodation in the post-operative groups. These findings suggest that MAC has contributions from the spinal cord as well as higher brain centers and that spinal cord reflexes may play a large role in the determination of MAC.

References:

1. Anesthesiology 26:756-63.
2. Anesthesiology 40:52-4.