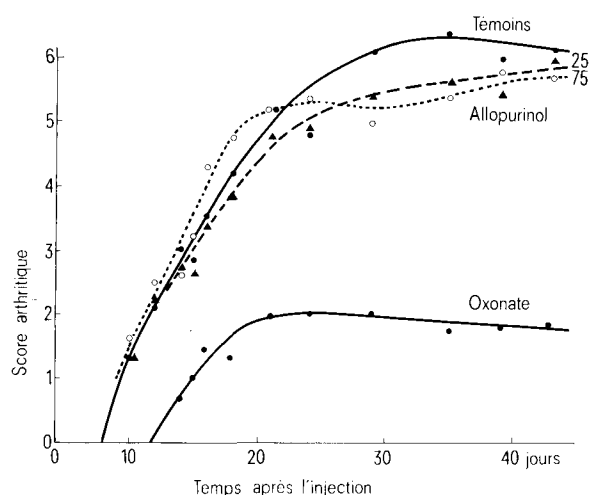


Influence de l'oxonate de potassium et de l'allopurinol sur l'arthrite à adjuvant*

Régime	Œdème de la patte injectée		Œdème de la patte non-injectée	Score arthritique
	Jours 0-9	Jours 9-45	Jours 9-45	Jours 0-45
Normal	100	100	100	100
Allopurinol 25 mg/kg jour	92	97	97	90
Allopurinol 75 mg/kg jour	94	103	115	94
Oxonate	73	36	19	32

* Surfaces relatives des courbes montrant l'évolution de l'œdème des pattes arrière et du score arthritique.



Variation du score arthritique chez les rats témoins (● — ●, courbe supérieure), les rats à l'oxonate (● — ●, courbe inférieure) et les rats à l'allopurinol (▲ — ▲, 25 mg/kg jour et ○ — ○, 75 mg/kg jour).

(inflammation de la patte injectée) et de la réaction secondaire (polyarthrite induite) a été suivie pendant 6 semaines par la mesure du poids des animaux, du volume des pattes arrière et d'un score arthritique. Les rats non-injectés ont servi de référence pour le volume des pattes. **Résultats.** L'injection d'adjuvant produit un accroissement rapide du volume de la patte injectée chez tous les rats injectés. La polyarthrite périphérique se développe après une période de latence d'environ 9 jours chez les rats témoins et chez les rats à l'allopurinol et de 13 jours chez les rats à l'oxonate (figure). Pour faciliter les comparaisons, nous avons mesuré (tableau) les surfaces relatives des différentes courbes (score arthritique et œdème des pattes arrière injectées et non-injectées) en prenant pour référence le groupe témoin injecté. L'oxonate a une légère action anti-inflammatoire sur la réaction primaire non spécifique (réduction de 27% de l'œdème de la patte injectée) et présente un effet immunosuppresseur important sur la polyarthrite (réduction de 64 et de 85% de l'œdème des pattes arrière injectées et non-injectées, réduction de 68% du score arthritique).

Les pertes de poids au cours des réactions primaire et secondaire sont plus faibles pour le groupe de rats à l'oxonate (10 et 27 g par rat) que pour les 3 autres groupes (32 et 65 g). Chez ces 3 derniers groupes uniquement, une ankylose de la colonne vertébrale caudale apparaît au cours de la 3^e semaine qui suit l'injection. Cette spondylite atteint environ 80% des animaux entre le 30^e et le 40^e jour.

Dans une expérience de courte durée (4 jours), Riesterer et Jaques⁹ ont montré que l'allopurinol n'a pas d'effet anti-inflammatoire sur l'arthrite à adjuvant déjà établie. Nos expériences montrent qu'il n'a pas non plus d'influence sur le développement de cette polyarthrite, même lorsqu'il est administré quotidiennement à des doses subléthales pendant plusieurs semaines. Il semble donc que le métabolisme des pyrimidines ne soit pas impliqué dans le mécanisme de l'inhibition de l'arthrite à adjuvant par l'oxonate.

9 L. Riesterer et R. Jaques, *Pharmacology* 2, 288 (1969).

LSD: The distribution of [³H]LSD in the reproductive system of the male rat and placental transfer in the female rat

D. J. Back and J. K. G. Singh

Department of Pharmacology and Therapeutics, University of Liverpool, Ashton Street, P. O. Box 147, Liverpool L69 3BX (England), 14 September 1976

Summary. After administration of [³H]LSD to male rats, radioactivity was present in all tissues of the reproductive system, notably associated with spermatozoa in the epididymis. In addition, in pregnant rats LSD and/or metabolites readily crossed the placental barrier.

The general distribution of LSD in mice and rats has been studied by several workers¹⁻⁶. The purpose of the present investigation was to study a) the distribution of [³H]LSD in the tissues of the reproductive system of the male rat and b) the placental transfer of [³H]LSD in late pregnancy. **Materials and methods.** Experiment 1. Mature male rats of the Wistar strain (250-350 g) were anaesthetized with urethane (14% w/v in 0.9% saline; 10.0 ml/kg i.p.). Polyethylene catheters were inserted into a femoral vein and a carotid artery. [2(n)-³H]lysergic acid diethylamide ([³H]LSD; specific radioactivity 15.8 Ci/mmole; obtained from the Radiochemical Centre, Amersham) was dissolved in saline : methanol (19 : 1 v/v) after evaporation of the organic vehicle. Radiochemical purity was shown to be 97% by thin layer chromatography in solvent

system chloroform : methanol : acetic acid (40 : 30 : 30). [³H]LSD (24 μCi/kg; 0.5 μg/kg) was injected i.v. and blood samples obtained prior to autopsy at 30, 60 or 180 min.

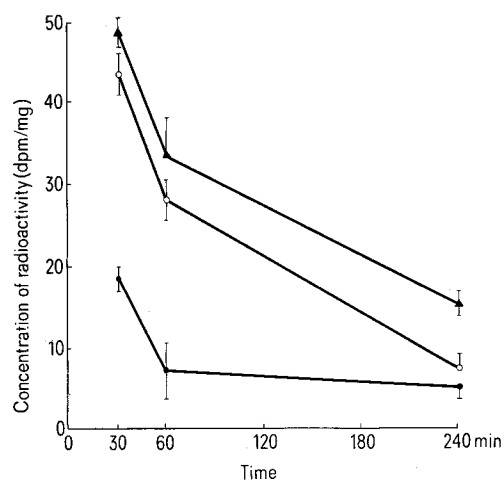
- 1 E. S. Boyd, E. Rothlin, J. F. Bonner, I. H. Slater and H. C. Hodge, *J. Pharmac. exp. Ther.* 173, 6 (1955).
- 2 A. Stoll, E. Rothlin, J. Rutschmann and W. R. Schalch, *Experientia* 11, 396 (1955).
- 3 J. Axelrod, R. O. Brady, B. Witkop and E. V. Evarts, *Ann. N. Y. Acad. Sci.* 66, 435 (1957).
- 4 E. S. Boyd, *Archs int. Pharmacodyn. Ther.* 120, 292 (1959).
- 5 J. E. Idanpaan-Heikkilä and J. C. Schoolar, *Science* 164, 1295 (1969).
- 6 I. M. Diab, D. X. Freedman and L. J. Roth, *Science* 173, 1022 (1971).

Epididymal fluid was collected as previously described⁷, and separated into epididymal plasma and spermatozoa by centrifugation at $12,000 \times g$ for 45 min in a micro-haematocrit centrifuge (Hawksley Ltd). At autopsy, the following organs were removed and weighed: seminal vesicles, coagulating gland, prostate gland, epididymides, testes and ductus deferentes. The epididymides were divided into caput, corpus and caudae epididymides. A known weight of each organ was taken, solubilized with NCS tissue solubilizer (Amersham/Searle: 0.5 ml) for

Distribution of radioactivity (dpm/g) in the reproductive system of the male rat at various times after i. v. administration of [³H]LSD (24 μ Ci/kg b. wt)

Tissue	Time (min)		
	30 (n = 3)	60 (n = 4)	180 (n = 3)
Blood plasma	42440 $\pm$ 1370	35480 $\pm$ 1850	27200 $\pm$ 3370
Epididymal plasma	8340 $\pm$ 2440	9000 $\pm$ 2450	18500 $\pm$ 3580
Spermatozoa	10520 $\pm$ 590	13750 $\pm$ 1600	14870 $\pm$ 2440
Seminal fluid	13420 $\pm$ 1300	16250 $\pm$ 960	13060 $\pm$ 1370
Seminal vesicle	31200 $\pm$ 2090	31670 $\pm$ 1030	23940 $\pm$ 3100
Coagulating gland	27930 $\pm$ 1300	39750 $\pm$ 2040	26120 $\pm$ 4930
Prostate gland	51510 $\pm$ 4800	49500 $\pm$ 4530	21230 $\pm$ 1580
Caput epididymides	42640 $\pm$ 5090	47000 $\pm$ 5690	30470 $\pm$ 3390
Corpus epididymides	74360 $\pm$ 27650	54670 $\pm$ 2490	31190 $\pm$ 4453
Cauda epididymides	33360 $\pm$ 7230	21330 $\pm$ 1030	19560 $\pm$ 1860
Seminiferous tubules	23580 $\pm$ 1960	27000 $\pm$ 1120	14510 $\pm$ 1660
Vas deferens	50650 $\pm$ 17940	30670 $\pm$ 1030	21400 $\pm$ 1080

Each value represents the mean $\pm$ SEM; n = number of animals.



Distribution of radioactivity in the placenta (▲-▲) foetus (●-●) and maternal blood plasma (○-○) after i.v. administration of [³H]LSD (24 μ Ci/kg b. wt) to 18 day pregnant rats. Each point represents the mean $\pm$ SEM of 3 experiments.

12 h and the radioactive content determined by liquid scintillation spectrometry⁸.

Experiment 2. 18 day pregnant Wistar rats were anaesthetized as previously described and catheters inserted into a femoral vein and carotid artery. [³H]LSD (24 μ Ci/kg) was administered i.v. and blood samples obtained prior to autopsy at 30, 60 or 240 min. At autopsy, both uterine horns were removed, and each foetus weighed and homogenized. A known weight of each placenta and foetal homogenate was solubilized and the radioactive content determined.

Results and discussion. The distribution of radioactivity in the male reproductive system after i.v. administration of [³H]LSD is shown in the table. All tissues contained LSD and/or metabolites. The concentration of radioactivity in epididymal plasma and spermatozoa was greater at 180 min than at 60 min. In contrast, in all other tissues the concentration at 180 min was less than at 60 min. In most tissues the concentration of radioactivity approximated to that in blood plasma.

These experiments clearly show that LSD and/or metabolites is distributed in the male accessory sex organs. Moreover, the presence of radioactivity has been shown both in the seminiferous tubules, where spermatozoa are being formed, and associated with spermatozoa undergoing maturation in the epididymis. These findings raise the interesting question as to whether or not LSD and/or metabolites is actually present within the sperm nucleus, and if so whether the presence of the drug could adversely influence spermatozoa development and maturation.

Radioactivity present in maternal blood plasma, placental tissue and the foetus at different time intervals is shown in the figure. The concentration, highest in the placenta, declined between 30 and 240 min. The percentage of administered radioactivity recovered per foetus was as follows: 0.11 $\pm$ 0.01% (mean $\pm$ SEM) at 30 min; 0.04 $\pm$ 0.02% at 60 min; 0.03 $\pm$ 0.01% at 240 min. Autoradiographic studies on the placental transfer of LSD in mice⁹ have indicated that in late pregnancy 0.5% of the radioactive dose passed the placental barrier into the foetus in 5 min. The teratogenic effects observed in rats when LSD was injected in early pregnancy^{9,10} indicate placental transfer in this species. The present experiments have confirmed this and demonstrated the appearance of a significant fraction of the dose in the near-term foetus.

- 7 D. J. Back, J. C. Shenton and T. D. Glover, *J. Reprod. Fert.* **40**, 211 (1974).
- 8 D. J. Back, *Steroids* **25**, 413 (1975).
- 9 G. J. Alexander, B. E. Miles, G. M. Gold and R. B. Alexander, *Science* **157**, 459 (1967).
- 10 G. J. Alexander, G. M. Gold, B. E. Miles and R. B. Alexander, *J. Pharmac. exp. Ther.* **173**, 48 (1970).

Anti-arthritis activity of bredinin, an immunosuppressive agent

H. Iwata¹, H. Iwaki², T. Masukawa, S. Kasamatsu and H. Okamoto²

Department of Pharmacology, Faculty of Pharmaceutical Sciences, Osaka University, 133-1, Yamada-kami, Suita-shi, Osaka (Japan), 30 August 1976

Summary. Bredinin has been found to have an inhibitory effect upon the secondary lesions occurring from adjuvant injection in rats.

Bredinin, a nucleoside antibiotic isolated from *Eupenicillium brefeldianum*, was found to have potent immunosuppressive effects, causing suppression of both primary and secondary immune responses in mice³. With respect to the mechanism of the immunosuppressive action of

bredinin, Sakaguchi et al.^{4,5} reported a growth inhibitory action of bredinin on mammalian cells due to blockade of the pathway from inosine 5'-monophosphate to xanthosine 5'-monophosphate or from xanthosine 5'-monophosphate to guanosine 5'-monophosphate. Recently,