Tumours of the nervous system induced in rats by single neonatal administration of N-ethyl-N-nitrosourea

Authors	Dose (mg/kg)	Rats injected	Rats with tumours	Nervous-system tumours				Other tumours	Days to first tumour	Median induction time (days)
				Brain	Cord	Cranial nerves	PNS			
Druckrey, Schagen and Ivankovic[8]	5	28	9 (32%)	8	1	0	0	0	238	500
Druckrey, Schagen and Ivankovic[8]	10	16	11 (69%)	2	2	10	7	0	161	310
Druckrey, Schagen and Ivankovic[8]	20	16	16 (100%)	3	6	13	12	1	187	240
Jones, Searle and Smith[9]	10	34[a]	33 (97%)	53	9	7	2	8	197	392

[a] Excluding 4 dying very early.

res, where all but 6 of the brain tumours occurred. Histologically, the most common tumours were subependymal-plate gliomas (17) and oligodendrocytomas (10). There were 9 tumours in the spinal cord. Of the 9 tumours (13%) in the peripheral nervous system, 7 were situated in the cranial nerves and their ganglia.

The only direct comparison possible with our results is afforded by the experiments of Druckrey, Schagen and Ivankovic[8], who employed neonatal administration of ENU over the dose range 5–80 mg/kg and also investigated the effects of administration at 10 and 30 days of age.

As is seen from the Table, using the same dose and age at administration as Druckrey et al., our proportion of treated animals developing nervous-system tumours was markedly greater (97%), though the median induction time was longer. Our animals developed relatively fewer tumours of the cranial and peripheral nerves but more spinal and very many more brain tumours. Though Druckrey et al. obtained a relatively higher proportion of brain tumours at 5 mg/kg only 32% of these rats developed tumours. Similarly, when a high proportion of brain tumours occurred following repeated i.v. administration of MNU[4], only 66% of animals developed nervous-system tumours.

A possible reason for the higher yield of brain tumours in our experiment is our use of non-pure-line albino and hooded rats of the types which are widely distributed and used, whereas Druckrey et al. used pure line BD-IX rats which have been inbred for very many years. Though the influence of dietary differences cannot of course be excluded, our results suggest that albino or hooded rats, treated once neonatally with ENU at about 10 mg/kg, may be considerably more useful as a source of brain tumours for therapeutic and other studies than is apparent from the existing literature.

Several points should be stressed. The usefulness of chemically induced tumours for various studies depends on the development by the animals of well-defined signs, such as paralysis or marked loss of weight due to the tumours, but sudden haemorrhage into a tumour occasionally causes death of an animal prior to the appearance of such signs. Moreover, 9 of the 53 brain tumours in our series were microtumours only found on histological examination.

Our preliminary results at higher dosages (25 and 50 mg/kg) accord with published work in that, although the latent period is shortened, a higher proportion of peripheral nerve tumours then develop. The effect of dividing these larger doses over several days on the proportions of tumours induced might well be of interest.

Zusammenfassung. Durch einmalige Verabreichung von 10 mg/kg N-Äthyl-N-Nitrosoharnstoff am 1. Tag nach der Geburt wurden bei 33/34 Ratten 53 Hirntumoren, 9 Tumoren des Rückenmarkes, aber nur 9 im peripheren Nervensystem erzeugt, was eine bedeutend gesteigerte Rate von Hirntumoren bedeutet.

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[10] We thank Miss Mary Trumper and Miss Valerie Nash for technical assistance and the Cancer Research Campaign for financial support of C.E.S.

Action of Tobacco on Lipolysis and its Modification by Insulin

The ability of nicotine to release catecholamines and therefore to stimulate lypolysis is well known. The purpose of this communication was to investigate the effect of smoking on plasmatic free fatty acid (FFA), and its modification by previous insulin treatment.

Methods. 15 smoking men (10–15 cigarettes a day) and 15 non-smoking men were tested. None of them were ill or under treatment that could influence the basal levels and behavior of the FFA. All of them fasted and lay in bed for 12 h before the test. Basal levels of FFA in both groups were determined initially and after smoking 2 black tobacco cigarettes with and without the inhalation of the smoke. Finally the experiment was repeated after the administration of 10 IU of insulin. The concentration of FFA in plasma has been determined by the method previously described by Dole and Meinertz[1].

Results. The results are shown in the Table; a significant elevation of FFA in smokers can be observed in

A) Lipolytic action of the tobacco measured by the behavior of the plasmatic free fatty acids (FFA) and expressed in μEq/l, average of 15 smokers and 15 non-smokers

No.	FFA μEq/l	Difference + significance
15 Smokers	715,600 ± 53,018	277,400 (38,764%) $P < 0{,}001$
15 Non-smokers	438,200 ±30,790	

B) FFA after smoking 2 cigarettes with inhalation of the smoke in 15 smokers and 15 non-smokers

Time (min)	Smokers		Non-smokers	
Basal	748,933 ± 51,418		438,200 ± 30,682	
10	963,866 ± 56,788	$(P < 0{,}01)$	506,333 ± 36,542	$(0{,}10 < P < 0{,}20)$
30	843,466 ± 45,568	$(0{,}10 < P < 0{,}20)$	494,400 ± 36,266	$(0{,}20 < P < 0{,}30)$
60	702,266 ± 43,454	$(0{,}40 < P < 0{,}50)$	428,733 ± 17,255	$(0{,}70 < P < 0{,}80)$

C) FFA after smoking 2 cigarettes without inhalation of the smoke in 15 smoking and 15 non-smoking men

Time (min)	Smokers		Non-smokers	
Basal	722,800 ± 47,785		455,800 ± 27,467	
10	878,400 ± 50,237	$(P < 0{,}02)$	594,600 ± 29,118	$(P < 0{,}05)$
30	786,066 ± 48,341	$(0{,}30 < P < 0{,}40)$	486,733 ± 25,436	$(0{,}40 < P < 0{,}50)$
60	747,800 ± 44,529	$(0{,}70 < P < 0{,}80)$	470,800 ± 30,354	$(0{,}70 < P < 0{,}80)$

D) FFA after smoking 2 cigarettes with inhalation of the smoke in 15 smoking and non-smoking men previous treated with 10 IU of insulin

Time (min)	Smokers		Non-smokers	
Basal	721,733 ± 45,568		469,666 ± 17,372	
10	802,266 ± 42,459	$(0{,}20 < P < 0{,}30)$	482,533 ± 18,271	$(0{,}60 < P < 0{,}70)$
30	763,133 ± 41,744	$(0{,}50 < P < 0{,}60)$	485,066 ± 17,656	$(0{,}50 < P < 0{,}60)$
60	727,000 ± 39,777	$(0{,}90 < P < 0{,}95)$	472,666 ± 16,260	$(0{,}90 < P < 0{,}95)$

comparison with non-smokers. Marked elevation of FFA is seen in smokers after 10 min of smoking 2 cigarettes with and without inhalation of the smoke. There is an increment of FFA in non-smokers after 10 min without inhalation. The previous administration of 10 IU of insulin inhibits the increment of FFA levels induced by the tobacco. The increment of FFA is significant only after 10 min interval between the act of smoking and the evaluation of the test, but it is not so after 30 min, or after 60 min.

Discussion. According to the above-mentioned results the smokers have significantly higher FFA basal levels than non-smokers (GOFMAN and LINGREN[2]; KERSBAUM[3]; DOYLE[4]). The inhalation of the smoke of 2 cigarettes in habitual smokers increases significantly FFA basal levels after 10 min; this does not happen in the non-smokers. The lipolytic action of tobacco seems to be more evident in the smokers than in the non-smokers. Smoking without inhalation of the smoke produces an increase of FFA after 10 min in both groups; this suggests an absortion of nicotine by oral mucosa. The reason why the increment of FFA is produced in the non-smokers after smoking without inhalation and not after smoking with inhalation is difficult to explain. The inhibition of the increment of FFA after smoking with previous administration of insulin, is due to the interference of the hormone in the action of catecholamines on the adipose tissue.

Resumen. Los fumadores habituales tienen niveles de FFA significantivamente más altos que los no fumadores. El acto de fumar incrementa la lipolisis. Fumar sin inhalar el humo produce incremento de lipolisis. La insulina inhibe la accion lipolítica del humo de tabaco.

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