N-METHYL-*N*-NITROSOUREA AS A MAMMARY CARCINOGEN: PRACTICAL APPLICATION

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Introduction: *N*-methyl-*N*-nitrosourea (MNU) is the oldest member of the nitroso compounds. It is considered a complete, potent and direct alkylating compound, able to alkylate the DNA without metabolic activation. The administration of chemical carcinogens is one of the most frequently used methods to induce tumors' development in laboratory animals. The target organ depends on the animals' species, strain and age, dose and route of administration (1-3). This work intended to describe the effects of MNU administration in female Sprague-Dawley rats.

Material & Methods: Procedures followed the European legislation and were approved by the Portuguese Competent Authority (approval nº008961). Twenty-five female Sprague-Dawley rats were used in two experimental protocols. The first experiment intended to evaluate the effects of exercise training on mammary carcinogenesis (n=15) and the second one intended to evaluate the effect of ketotifen on mammary carcinogenesis (n=10). At seven weeks of age, all animals were intraperitoneally injected with the carcinogen MNU (50 mg/kg). Mammary tumors development was weekly assessed by palpation of both mammary chains. Animals were humanely sacrificed, through the intraperitoneal administration of ketamine and xylazine, 35 and 18 weeks after MNU administration, respectively.

Results: All animals from the first experiment and six animals from the second experiment developed mammary tumors (incidence of 100% and 60%, respectively). In the first experiment, the first mammary tumor was identified ten weeks after MNU administration. A shorter latency period was observed in the second experiment, with the development of the first mammary tumors eight weeks after MNU administration. At the end of the experiment, animals from the first experiment developed a total of 28 mammary tumors (28/15; 1.9 tumors/animal), while the animals from the second experiment developed 21 mammary tumors (21/6; 3.5 tumors/animal). At the same time (18 weeks after MNU administration), the animals from the first experiment developed only five mammary tumors.

Conclusions: Although the carcinogen was administered to the animals of the same strain at the same age and dose, using the same route, the latency period and incidence were different between the experiments. The different incidence may be related with the duration of the studies and the individual variations.

References: (1) Gullino PM et al. *J Natl Cancer Inst.* 1975; 54: 401-14; (2) Tsubura et al. *In Vivo*. 2011; 25: 11-22; (3) Faustino-Rocha et al. *Tumor Biol.* 2015; 36: 9095-117.

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