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# Increased neonatal mortality in offspring of male rats treated with methadone or morphine before mating

METHADONE ((±)-4, 4-diphenyl-6-dimethylamino-3-heptanone hydrochloride) is a potent (addictive) analgesic with pharmacological effects which are qualitatively similar to those of morphine, although it is far more effective than morphine when given orally. Its ability to diminish the severity of the abstinence syndrome resulting from heroin withdrawal led to the introduction of methadone in the chemotherapy of narcotic addiction[1–3]. Little is known, however, about its long term toxicity effects. We report that treatment of male rats with either (±)-methadone HCl (METH) or morphine sulphate (MS), given orally, for 24 h before mating to untreated females increases the neonatal (21-d) mortality of their offspring.

Sixty naive female Charles River (CD) albino rats (which had not been previously treated with the drug) were mated to 26 male rats which had received 13, 18 or 38 mg $kg^{-1}$ $d^{-1}$ METH during the previous 24 h. Another 60 naive female rats were mated to 26 other male rats similarly treated with 22, 47 or 55 mg $kg^{-1}$ $d^{-1}$ MS. Females were exposed to treated males for 7 consecutive days.

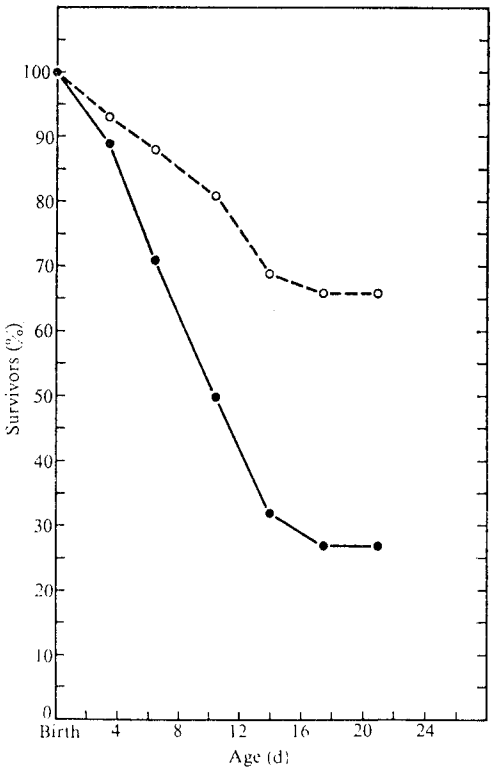


Fig. 1 Neonatal (21-d) survival of 166 live offspring sired by male rats pretreated with MS (○) and 145 live offspring sired by male rats pretreated with METH (●). Twenty-six per cent of the offspring sired by METH pretreated males and 66% of the offspring sired by the MS pretreated males survived. Of the live offspring of untreated males 90–95% survived for 21 d.

Figure 1 shows the marked difference in the 21-day mortality of the offspring. Those from MS-treated males (six fostered and ten unfostered litters) had 57 deaths out of 166 live births (34% mortality), whereas those from METH-treated males (seven fostered and seven unfostered litters) had 107 deaths out of 145 live births (74% mortality). This difference is very significant ($\chi^2 = 46.77$, $P < 0.001$). The METH offspring ($n = 145$) died at the rate of 8 per day from days 4 to 14, whereas the MS offspring ($n = 166$) died at a rate as high as 6 per day only between days 11 and 14, suggesting that a different lethal mechanism is operating. Overall mortality in both groups is considerably greater than the 5.9% rate in 1,645 offspring resulting from matings of untreated males and females, and reared by untreated foster mothers[4,5].

We also investigated the effects of pretreating male rats for 24 h with METH given 0–24 h or 25–48 h before mating with naive females ($n = 12$ in each group). Males were first placed in a cage and provided with a 5% sucrose drinking water solution containing 0.67 mg $ml^{-1}$ or 0.067 mg $ml^{-1}$ METH. The 'high-dose' METH males received 52 mg $kg^{-1}$ $d^{-1}$, the 'low-dose' METH males 25 mg $kg^{-1}$ $d^{-1}$. A third group received sucrose solution alone. Each male remained in this cage with four females for 24 h. (The offspring of these females are not part of the present study.) Males were then moved to a second cage provided with drinking water with neither drug nor sucrose, containing four drug-naive females, the offspring of which are identified as the '0–24 h' offspring, as the males had received METH in that period prior to siring these offspring. After 24 h with these females each male was then moved to a third cage provided with pure drinking water and containing

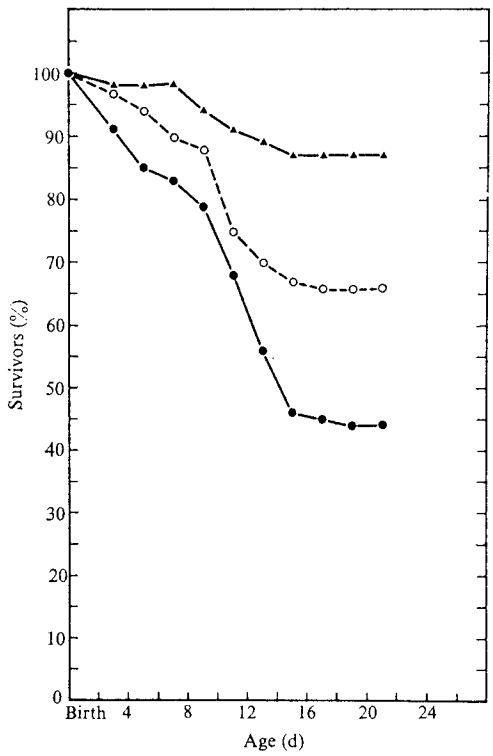


Fig. 2 The 21-d survival of the offspring of naive females mated with male rats pretreated with either no drug (▲) or with low-dose METH (○, 25 mg $kg^{-1}$ $d^{-1}$) or high-dose METH (●, 52 mg $kg^{-1}$ $d^{-1}$) during the 24-h period before mating. These three mortality rates differ significantly ($P < 0.01$) from each other.

four more naive females, the offspring of which are identified as the '25–48 h' offspring. After 24 h with these females each male was then returned to the initial cage containing the drinking water with 5% sucrose solution (with or without METH) and the cycle repeated. Each naive female was exposed to males for 6 consecutive days.

The neonatal (21-day) mortality of the offspring of the three groups of males is shown in Fig. 2. In 21 days, 13% of 132 offspring sired by control males died, whereas 56% of 100 offspring sired by high-dose METH males died (difference very significant: $\chi^2 = 47.08$, $P < 0.001$) and 34% of 100 progeny of low-dose METH males died (difference from controls significant: $\chi^2 = 13.59$, $P < 0.01$, and from high-dose of METH progeny: $\chi^2 = 8.91$, $P < 0.01$). The neonatal mortality of 244 offspring of males which had received METH 25–48 h before mating was only 25%. This did not differ significantly ($\chi^2 = 3.41$, $P > 0.05$) from the 21-day mortality of their controls (17%). Of the ten litters sired by control males only one had a death rate in excess of 30% (Fig. 3), whereas of the eight litters sired by the high-dose METH males, six litters lost 40% or more of the offspring born alive. The low-dose methadone litters had a smaller death rate than the high-dose METH offspring. These data demonstrate that the increased mortality of the METH-sired offspring is not simply a consequence of the deaths of the offspring of a small proportion of the males, but of an increased mortality in virtually all litters.

Pretreatment of male rats with METH before mating thus produces a significant increase in neonatal (21-day) mortality of the offspring of the METH-treated males and naive females when compared to control matings. Our data show a dose-response relationship for this phenomenon as well as evidence

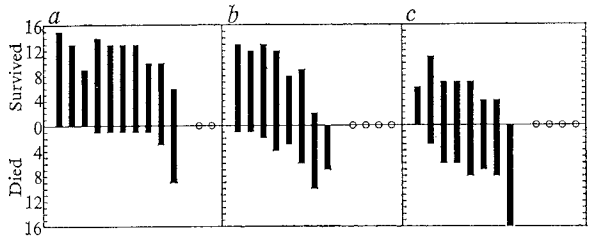


**Fig. 3** Survival and death in each litter of offspring born to females mated to (*a*) controls and males receiving (*b*) low- and (*c*) high-dose METH 0–24 h before mating. The vertical black bars show the survival or death of the live offspring from each litter. ○, Females which did not deliver offspring.

that the lethal effect is seen primarily in offspring sired during the first 24 h following administration of METH to the male. Morphine produced a similar but less marked effect. An urgent problem in medicine is the fact that 1–3% of all infants born have one or more unexpected congenital anomalies which cannot be explained by classical teratology. Our preliminary results suggest that it is necessary to investigate not only the drugs which were administered to the mother before and during pregnancy, but also those drugs used by the father. This approach may contain the answers to some of the unexplained problems of childhood growth and development.

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# Physiology of visual cells in mouse superior colliculus and correlation with somatosensory and auditory input

THE two main targets of the mammalian optic nerve fibres are the lateral geniculate body and the superior colliculus (optic tectum). From studies with various techniques, and in several mammalian species including the cat[1-5], monkey[6-9], rabbit[10-12], rat[13], and ground squirrel[14] three major functions of the superior colliculus have been described. In the superficial layers the visual input is processed in a specific way; in deep layers several sense modalities, chiefly visual, auditory and somatosensory, are brought together; stimulation of the tectum results in an orienting of the animal's eyes, head or body towards a location corresponding topographically to the part of the tectum stimulated.

Gordon[1] has shown that for a given location in the cat tectum there is a good correlation between the positions of visual receptive fields and the directions from which maximal auditory responses are evoked. She also found a correlation between preferred directions of stimulus movement in the two modalities. The agreement between visual and somatosensory cells was much looser, although visual receptive fields near the vertical midline were correlated with tactile fields on the face, and temporal visual fields, with tactile fields on the body or legs. She rarely observed responses from whiskers. Cats move their eyes and especially their heads extensively, however, and a very close relationship between retinotopic and somatosensory maps was perhaps not to be expected.

We have studied the superior colliculus in the mouse, a small compact animal with very little eye movement and relatively little head movement; a mouse rather turns its whole body towards an interesting object. The major part of the mouse's visual field is crossed by an elaborately developed somatosensory organ, the vibrissae. Whisker movement in the mouse is very rapid, but the excursions are small, so that the whiskers bear a relatively constant relationship to the visual field. One should therefore not be surprised to find a close topographical relationship between the tectal projections from retina and whiskers.

In our study, ten mice of the C57BL/6J strain were used. Throughout the experiment a mouse was kept under light anaesthesia (pentobarbital and chlorprothixene) and was neither paralysed nor artificially respirated. (For exact procedures, see Dräger[15].) The head was held fixed by means of a small metal block glued to the skull, thus leaving the ears free. Visual receptive fields were mapped on a translucent tangent screen placed at a distance of 10.5 cm from the mouse. Electrolytically polished tungsten electrodes were used for recording. Electrode tracks, most of which were perpendicular to the tectal surface, were marked by several small electrolytic lesions (2 μA for 2 s) and reconstructed histologically. A total of 323 recordings were made in 48 penetrations. Of these records, 145 were probably from tectal cells. The remaining 178 recordings, from unit clusters or poorly resolved units, were useful for purposes such as topographical mapping of the tectal surface.

Cells in the superficial layers had small visual receptive fields (average diameter 9°) whose locations in the visual field varied according to a topographical map similar to that described for other vertebrates[16]: the nasal visual field projected anteriorly and the upper visual field medially. These cells responded only to visual stimulation, with best responses to a slowly moving small spot of any shape. One-quarter of the cells preferred one direction of movement; for most cells the preferred direction was upward. Deeper in the tectum most visual cells had very different receptive-field properties, with large fields (20°–60°), sluggish and transient responses to small moving objects, little or no response to large stimuli, and often a directional selectivity with preference for upward movement. Characteristically these deeper-layer cells tended