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Synaptic behaviour of some structural and numerical chromosome anomalies in female and male rats (*Rattus norvegicus*)

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Summary. The processes of synapsis and synaptic adjustment have been detected in some structural and numerical anomalies in two female rat foetuses and in one male rat in the course of a study on X-ray genotoxicity.

The synaptic characteristics and adjustment of one pericentric inversion and a deletion have been analysed by electron microscopy in synaptonemal complex spreads from two female foetuses, and the synaptic behaviour of a trisomy has been studied in a testicular biopsy from an adult male. In a large proportion (from 50% to 90%) of the analysed cells, the abnormal meiotic configuration could not be detected either because the anomaly was present in mosaic from trisomy or because synaptic adjustment had already taken place (inversion) or as result of a combination of two of the above (deletion).

Key words: Meiosis, Synaptic adjustment, Synaptonemal complexes

Introduction

Synapsis is a complex process that takes place during the prophase of the first meiotic division and includes homology search, homology check-up, and eventually, recombination. After legitimate pairing, which occurs during lepto-zygotene, illegitimate (non-homologous) pairing is allowed.

In carriers of structural reorganisations, synapsis may produce complex meiotic configurations resulting in the production of simple (deletions, duplications) or complex (inversions, insertions) loops or multivalents (translocations). However, these configurations may only be detected during early prophase I because after mid pachytene, and as a result of the process of synaptic adjustment (illegitimate pairing), some of the more conspicuous meiotic configurations (loops, double loops, multivalents) may disappear and the anomaly go undetected.

Although synaptic adjustment does not always take place, it has been documented in paracentric and pericentric inversions (Ashley et al., 1981; Davisson et al., 1981; Poorman et al., 1981a; Moses et al., 1982; Vidal et al., 1982a; Moses and Poorman, 1984; Saadallach and Hulten, 1986; Tease and Fisher, 1986), in Robertsonian and reciprocal translocations (Moses, 1979; Vidal et al., 1982b, 1987; Templado et al., 1984; Bogdanov et al., 1986, de Boer et al., 1986; Navarro et al., 1986; Grao et al., 1989), deletions and duplications (Moses and Poorman 1981; Poorman et al., 1981b), insertions (Mahadevaiah et al., 1984) and in different types of heteromorphisms (Hale and Greenbaum 1988a,b; Sharp, 1986). The reason for synaptic adjustment seems to be related to the fact that lineal, whole paired bi-multivalents are more stable than abnormal configurations (Moses and Poorman, 1981; Moses et al., 1982; Vidal et al., 1982a,b) and do not delay anaphase (Guitart et al., 1987).

Meiotic exchanges may produce unbalanced gametes, with different combinations of more or less complete duplications and/or deficiencies (White 1973; Davisson et al., 1981; Moses and Poorman, 1981, 1984; Moses et al., 1982; Mahadevaiah et al.,1984; de Boer et al., 1986) that result in a reduced fertility of the affected individual.

During our studies of genotoxicity of radiation in the rat (*Rattus norvegicus*) we have detected some spontaneous or induced chromosome anomalies in female and male animals. In this paper we describe the synaptic behaviour of a pericentric inversion and a deletion in female rat foetuses and a trisomy in an adult male rat.

Material and methods

The chromosome abnormalities analysed were detected in some of our specimens during a synaptic

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study of genotoxicity of X-rays on female rats and during a comparative study of the synaptic process on male and female rats.

The study was carried out on oocytes from one female rat foetus carrier of a pericentric inversion and one female rat foetus carrier of a deletion, both studies on day 20 of gestation, and on spermatocytes from a trisomic 90 day-old male rat, obtained from a testicular biopsy.

Synaptonemal complex (SC) spreads were obtained by cytocentrifugation (Martínez-Flores et al., submitted). Briefly, oocytes and spermatocytes were cytocentrifuged (10 min, 112g) in hypotonic solution (sucrose 0.1M) on formvar-coated slides (Navarro et al., 1981) and air-dried for 3 hours. Afterwards, they were fixed in a 9% formaldehyde solution in distilled water (pH 10) for 20 min. The slides were rinsed in several baths of distilled water and stained with silver nitrate for 60-90 min at 65 °C. SC spreads were cut out and placed on electron microscopy (EM) copper grids (Polaron G-50) for analysis (TEM, Hitachi H-7000).

Results

1. Pericentric inversion in a female rat foetus

During an SC study of X-ray genotoxicity in the rat, the presence of a pericentric inversion was observed in a female foetus obtained at 20 days of gestation from a rat that had been irradiated (5 Gy) 30 days before pregnancy (Martínez-Flores at al., 1998). A typical inversion loop was detected in 8.4% of pachytenes, although in earlier stages of meiosis the presence of the inversion (Fig. 1) was seen in 51.6% of the oocytes analysed (Table 1). Table 1 also includes the frequencies of the different configurations observed, that correspond to different stages of loop formation:

(a) Synaptic initiation (Fig. 2a-c). Synapsis began in one of the regions between the tip of the chromosome and of the inversion breakpoints (Fig. 2a). Afterwards, the equivalent segment on the opposite side of the chromosome also paired (Fig. 2b). The length of the inversion corresponded to approximately 38% of the length of the bivalent. The inverted region and its homologous segment remained asynaptic, but their middle regions got closer and were about to twist over their axis. In Figure 2c twisting had already occurred, and both centromeres were on the same side of the pre-loop.

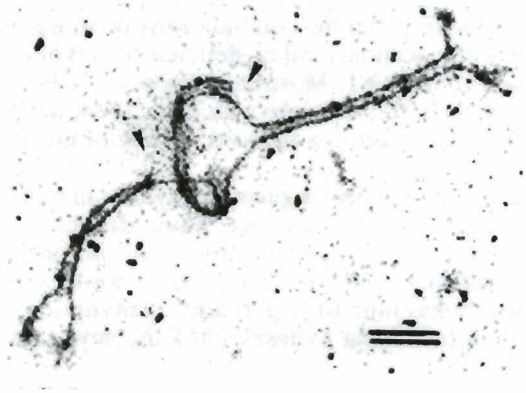

Fig. 1. Pericentric inversion in a female rat foetus. Inversion loop in a zygotene spread. The loop has a typical tridimensional aspect. Arrowheads indicate the tip of a broken lateral element and of a broken central element. The terminal regions of the SC are still unsynapsed. Electron microscopy (EM). Double bar: 1 μm.

(b) Synaptic progression (Fig. 2d) could be seen as an incipient loop formation, that will extend to both sides of the centromeres.

(c) Loop formation (Fig. 2e) was finally complete, and synapsis was now complete for the whole bivalent.

In a high percentage of cells, however, a loop could not be detected and all 21 SCs had a normal appearance (Fig. 2f).

2. Intercalary or terminal deletion in a female foetus

The presence of a deletion was detected in a female foetus obtained at 20 days of gestation from a non-irradiated rat (Martínez-Flores et al., 1998). Although no other studies than SC analyses were carried out, the deletion seemed intercalary because in some figures (Fig. 3a,b) a terminal plate seemed to be present in the deleted lateral element. The chromosome affected participated in the organisation of nucleolar structures (Fig. 3a) through one of its lateral elements, although the deleted element seemed to have lost the nucleolar organising region. The presence of nucleolar remains

Table 1. Meiotic configurations of the pericentric inversion depending on meiotic stage.

MEIOTIC STAGE		ZYGOTENE	PACHYTENE
Inversion undetectable		48.4%	91.6%
Inversion detected		51.6%	8.4%
Stage	Synaptic initiation	29.7%	0%
	Synaptic progression	18.8%	2.1%
	Loop formation	3.1%	6.3%
Total number of analysed oocytes		64	142

Table 2. Frequency of the different types of pairing observed in a terminal or intercalary deletion.

TYPE OF PAIRING		n	%
Normal		118	78.7
Deletion	Asynapsis	14	9.3
	Homologous synapsis	9	6
	Synaptic adjustment	9	6
Total number of cells		150	100

made observation difficult and Table 2 shows the number of oocytes in which the deletion could be well characterised. In many of the Figures, the deleted region was asynaptic (Fig. 3b). Loop formation in the normal

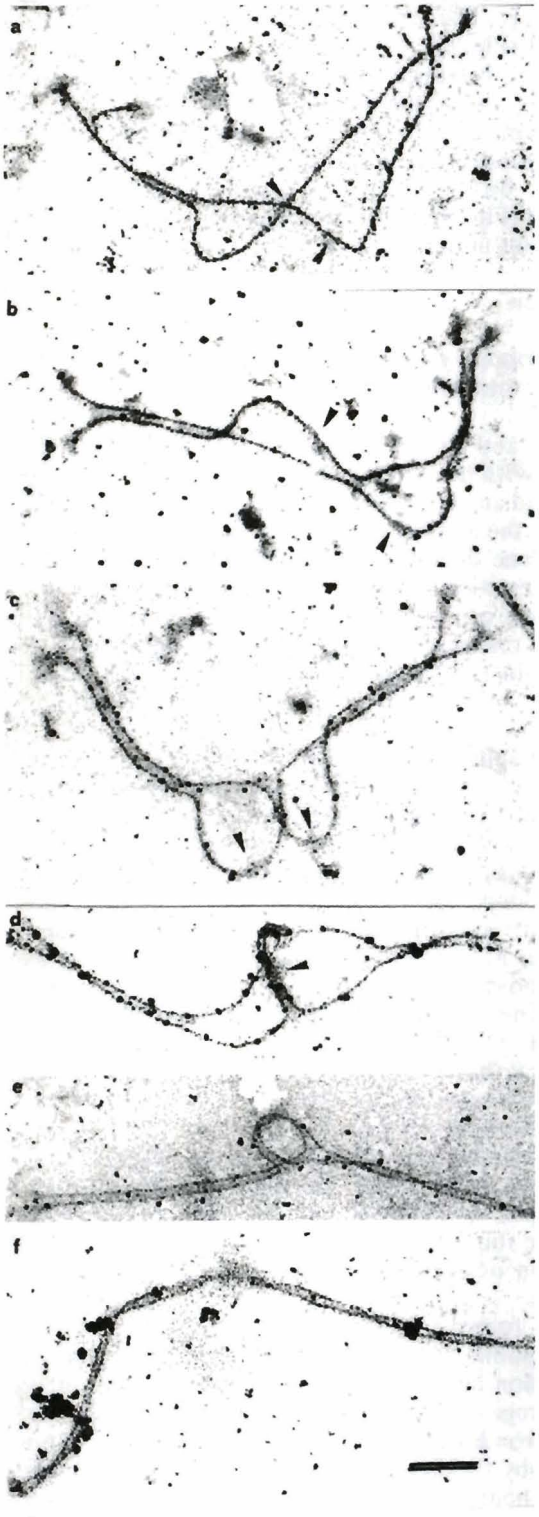

Fig. 2. Pericentric inversion in a female rat foetus. **a.** Synapsis begins on one side of the inversion. The opposite side and the tips of the chromosomes are still unsynapsed. Arrowheads indicate position of the centromeres. **b.** Synapsis has taken place on both sides of the inversion (arrows). The centre of the inverted segments is about to connect and twist. Arrowheads point to centromeres. **c.** The inverted region has already twisted over its axis. Both centromeres (arrowheads) are on the same side of the pre-loop. **d.**The inversion loop is beginning to extend, but centromeres (arrowhead) are still out of the loop. **e.** Complete loop formation with a bidimensional aspect due to spreading. (f) Bivalent without a loop, probably resulting from synaptic adjustment. Centromeres are in the center of the SC. (a-f) EM, Double bar: 1 μm.

Table 3. Number of spermatocytes and meiotic configurations in a mosaic trisomic male rat. Configurations A, B, D and E have been described by Speed (1984). Configurations C and F have not been previously described.

		n	%
Diploid		49	55.7
Trisomic	Type A	5	5.7
	Type B	13	14.7
	Type C	4	4.6
	Type D	13	14.7
	Type E	2	2.3
	Type F	2	2.3
Total number of cells		88	

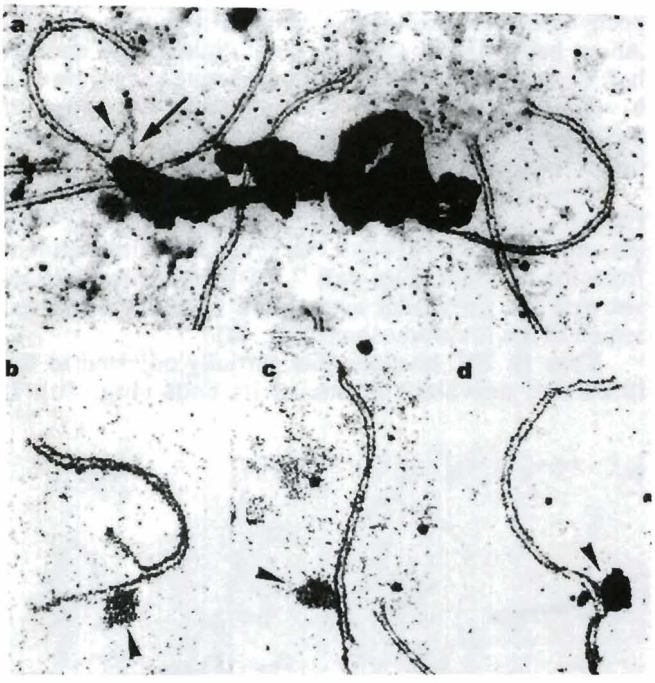

Fig. 3. Deletion in a female foetus. **a.**The deleted SC participates in the organisation of the nucleolus through one of its lateral elements (arrow), but the deleted (shorter) lateral element seems to have lost its nucleolar organising region (arrowhead). **b.** Asynapsis of the deleted region (arrow); remnants of nucleolar material are associated to the normal lateral element (arrowhead). **c.** Complete synapsis of the deleted region (arrow). Nucleolar material associated to the normal lateral element (arrowhead). **d.** Synaptic adjustment. The normal lateral element has thickened and adapted its length to the deleted lateral element (arrow). Nucleolar material associated to the normal lateral element (arrowhead). (a-d) EM. Bar : 5 μm.

lateral element was never observed. In other spreads, heterologous pairing had already been allowed, and the deleted region was fully synapsed (Fig. 3c). In a similar number of cells, synaptic adjustment had taken place: the normal lateral element had thickened and shortened to adapt to the length of the deleted element (Fig. 3d). In all cases, the normal lateral element was closely related to remnants of nucleolar material.

3. Trisomy in an adult male

During a comparative study of the synaptic process on female and male rats (Martínez-Flores et al., submitted), a mosaic trisomy was observed in a testicular biopsy from a 90-day-old adult male. 88 pachytenes were analysed in which all SCs were present. About half of them (55.7%) were diploid, and another half were trisomic (Table 3). The trisomic cells showed a bivalent plus univalent with six different types of meiotic configurations (Fig. 4a-g), some of them already described by Speed (1984).

Type A: Bivalent plus independent univalent. In this type of configuration, also described by Speed (1984), the univalent was always thickened and independent from the bivalent (Fig. 4a); 7.7% of these pachytenes showed the univalent associated with the unpaired region of the X chromosome (Fig. 4b).

Type B: The bivalent was partially adjusted to the thickened univalent at one of its ends (Fig. 4c). It corresponds to the Type B described by Speed (1984).

Type C: The bivalent was adjusted to the thickened univalent at both ends (Fig. 4d).

Type D: The bivalent was adjusted to the thickened univalent along all its length (Fig. 4e). It corresponds to the Type A described by Speed (1984).

Type E: Presence of a trivalent with partner exchanges (Fig. 4f).

Type F: Presence of a trivalent configuration after lineation of the partner exchanges (Fig. 4g).

In some diplotenes, the three axes of the chromosomes involved in the trisomy were close together, but only two of them were terminally associated (Fig. 4h). This configuration corresponds to a bivalent plus univalent association.

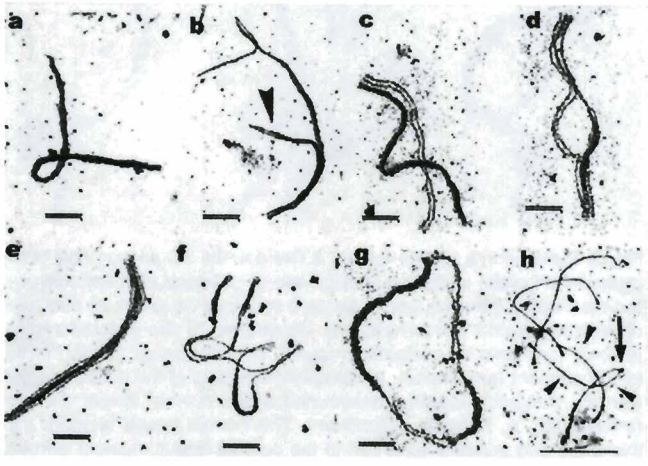

Fig. 4. Trisomy in an adult male. **a.** Isolated, thickened univalent in a trisomic male. **b.** In some cases, the thickened univalent is associated to the unpaired axis of the X chromosome (arrowhead). **c.** Bivalent with a thickened univalent adjusted at one of the ends (arrow). **d.** Bivalent with a thickened univalent adjusted at both ends, but not in the middle region. **e.** Bivalent with a thickened univalent adjusted along all its length **f.**Trivalent with partner exchange; the unpaired regions are thickened. **g.** lineation of a trivalent with partner exchanges; the thickened segments correspond to unpaired regions. **h.** Diplotene in a trisomic male. The axes of two chromosomes are terminally associated (arrow). Arrowheads show the three axes of the chromosomes involved in the trisomy. The axis of the third chromosome is close, but not associated with the other two. EM (a-g) Double bar = 1 μm, (h) Bar: 5 μm.

Discussion

1. Homologous pairing and synaptic adjustment in a pericentric inversion

Tease and Fisher (1986) observed female mouse foetuses with an inversion of the X chromosome (In (X)1H) and an autosomal inversion (In (2)2H), in which, with time, the number of cells showing an inversion loop at pachytene decreased from 28.7% and 26.2% at 15 days of gestation to 7.6% and 5.6% respectively at 19 days. However, the frequency of inversion loops in zygotene remained constant. This suggests that the decrease in the frequency of loops at pachytene is probably related to a phenomenon of synaptic adjustment.

Our results are in agreement with this conclusion, because the proportion of cells with an inversion loop at zygotene (51.6%) and at pachytene (8.4%) was similar to that described by Tease and Fisher (1986). The decrease may result from synaptic adjustment of the inversion loop. This phenomenon was first described for a pericentric inversion and for a tandem duplication by Moses and Poorman (1981) and by Moses et al. (1982) who proposed a mechanism of reverse synapsis to explain the heterosynaptic adjustment after mid-pachytene.

The evolution of the inverted segment through zygotene observed by us is similar to that described in mouse spermatocytes by Moses et al. (1982) and in human spermatocytes (Guichaoua et al., 1986; Gabriel-Robez et al., 1986, 1987; Batanian and Hultén, 1987). The synaptic initiation and synaptic progression stages take place during early and mid-zygotene, while loop formation occurs during late zygotene and early pachytene.

Loop formation requires at least three pairing-initiation points, two in the homologous regions flanking the inversion and one in the centre of symmetry of the inverted region (Moses et al., 1982; Guichaoua et al., 1986; Borondin et al., 1990). In our case, as in those described by Guichaoua et al. (1986) the initiation points are in the homologous regions, and only later is synapsis

established within the inverted segments. This would be the expected behaviour in most cases of inversion.

Also in agreement with Guichaoua et al. (1986), the double symmetry of the images observed by us with respect to the longitudinal and perpendicular axes of the bivalent suggest that reverse synapsis begins in the center of symmetry of the inverted segment, as should be expected from homology recognition.

Although our results suggest that synaptic adjustment takes place in this case, it may not be a universal phenomenon. Synaptic adjustment has not been observed in some cases, mainly in plants (Maguire, 1981; Anderson et al., 1988).

Loop formation is independent of the length of the inversion. If an inversion loop cannot be produced, the inverted regions will associate in heterosynapsis. Since heterosynapsis (illegitimate pairing) occurs after recombination has taken place, no unbalanced gametes would be produced (Chandley et al., 1987).

2. Synaptic adjustment in an intercalary deletion

In this case, our observations are in agreement with those of Moses and Poorman (1981). The lateral element corresponding to the normal chromosome adjusts its length to that of the deleted chromosome, and unpaired regions thicken. No deletion loop formation was observed in this case.

3. Synaptic adjustment in an autosomal trisomy

In mammals, data on the meiotic behaviour of trisomies by SC analysis are scarce (Wallace and Hultén, 1983; Johannisson et al., 1983; Speed, 1984; Power et al., 1992). The results show some of the theoretical configurations expected from an autosomal trisomy. In our case, some other configurations have also been observed.

The partial or complete adjustment of a thickened univalent and a normal bivalent may reflect a tendency to avoid univalent formation, although after lineation of the complete bivalent plus univalent this figure will be produced anyway. This triple adjustment has also been described in human trisomy 21 (Wallace and Hultén, 1983) or in the horse (Power et al., 1992).

Unpaired regions always appear thickened, as a result of an accumulation of homology recognition and mismatch repair proteins, specially the so-called "desperation proteins" equivalent to Rad 51 (Barlow et al., 1997)

Often, the extra chromosome, either unpaired or partially paired associates with the sex chromosomes, and specially with the axis of the X chromosome. According to Lifschytz and Lindsley (1972), this might interfere with X-chromosome inactivation and produce a meiotic arrest (Forejt et al., 1981). However, association of the sex chromosome with extra chromosomes or with asynaptic segments of normal or translocated chromosomes is not a universal phenomenon (Navarro et al., 1986; Grao et al., 1989). In our case, association of the univalent with the sex chromosome was only seen in 7.7% of nuclei.

The case of trisomy analysed by us was a case of mosaicism. Although in one case of trisomy 21, Johannisson et al. (1983) concluded that in many cells the extra chromosome was not visible because it was included in the sex vesicle, our results, as well as those of Hultén and Lindsten (1970), Kjessler and de la Chapelle (1971), Scröder et al. (1971) and Speed (1984) indicate that this is most unlikely and that cases with disomic/trisomic cells should rather be considered as germ line mosaics.

Synaptic adjustment, according to our results, is a common mechanism in female and male meiosis, and probably represents a tendency to substitute unstable configurations by more stable ones that will facilitate progression into anaphase I and prevent meiotic arrest.

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