X-4 Translocations and Meiotic Drive in *Drosophila melanogaster* Males: Role of Sex Chromosome Pairing

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ABSTRACT

Males carrying certain *X-4* translocations exhibit strongly skewed sperm recovery ratios. The X^P4^D half of the translocation disjoins regularly from the *Y* chromosome and the 4^PX^D half disjoins regularly from the normal *4*. Yet the smaller member of each bivalent is recovered in excess of its pairing partner, apparently due to differential gametic lethality. Chromosome recovery probabilities are multiplicative; the viability of each genotype is the product of the recovery probability of its component chromosomes. Meiotic drive can also be caused by deficiency for *X* heterochromatin. $In(1)sc^{4L}sc^{8R}$ males show the same size dependent chromosome recoveries and multiplicative recovery probabilities found in $T(1;4)B^S$ males. Meiotic drive in $In(1)sc^{4L}sc^{8R}$ males has been shown to be due to *X-Y* pairing failure. Although pairing is regular in the *T(X;4)* males, the striking phenotypic parallels suggest a common explanation. The experiments described below show that the two phenomena are, in fact, one and the same. *X-4* translocations are shown to have the same effect on recovery of independently assorting chromosomes as does $In(1)sc^{4L}sc^{8R}$. Addition of pairing sites to the 4^PX^D half of the translocation eliminates drive. A common explanation—failure of the distal euchromatic portion of the X chromosome to participate in *X:Y* meiotic pairing—is suggested as the cause for drive. The effect of *X* chromosome breakpoint on *X-4* translocation induced meiotic drive is investigated. It is found that translocations with breakpoints distal to 13C on the salivary map do not cause drive while translocations broken proximal to 13C cause drive. The level of drive is related to the position of the breakpoint—the more proximal the breakpoint the greater the drive.

A translocation between the *X* and fourth chromosomes ($T(1;4)B^S$) of *Drosophila melanogaster* was found by NOVITSKI and SANDLER (1957) to cause aberrant recovery of meiotic products in males. Although disjunction was regular—the *Y* always disjoined from X^P4^D and the normal fourth chromosome always disjoined from 4^PX^D—reciprocal meiotic products were not recovered equally. *Y* chromosome recovery was depressed relative to that of its pairing partner, the X^P4^D translocation half, while 4^PX^D was recovered in smaller numbers than the normal fourth chromosome. Chromosome recoveries were found to be multiplicative; that is, the viability of a genotype such as *Y;4* was the product of the recovery probabilities of its component chromosomes. Zygotic inviability seemed unlikely given the fact that it was the normal *Y* chromosome rather than the abnormal X^P4^D translocation half that exhibited poor recovery. NOVITSKI and SANDLER suggested a "meiotic drive" mechanism in which an asymmetric bivalent somehow led to preferential inclusion of one member in functional gametes. A subsequent study by ZIMMERING (1960) showed that another *X-4* translocation with a similar *X* breakpoint exhibited the same phenomenon.

Two other cases of meiotic drive induced by rearranged sex chromosomes are known in Drosophila. Males heterozygous for $In(1)sc^{4L}sc^{8R}$, an *X* chromosome missing most of the proximal heterochromatin, and a normal *Y* exhibit both substantial *X-Y* nondisjunction and skewed sex chromosome recovery ratios. Again it is the rearranged *X* chromosome rather than the normal *Y* that is favored. No evidence for zygotic mortality could be found (SANDLER and BRAVER 1954). Meiotic chromosome loss has been ruled out by light microscope analysis (COOPER 1964; PEACOCK 1965). Cytological evidence at both the light and electron microscope levels points to abnormal sperm development and sperm abortion as the likely mechanism (PEACOCK 1965; PEACOCK, MIKLOS, and GOODCHILD 1975). The second case involves certain attached-*XY* chromosomes that exhibit depressed recovery from males carrying the attached-*XY* and a free *X* duplication consisting of part or all of the *X* heterochromatin (LINDSLEY and SANDLER 1958). Disjunction is normal when the free duplication is large enough to include the pairing sites. Yet in some cases the free duplication is recovered in 70–80% of the sperm. No appreciable zygotic mortality has been observed. Since meiotic loss can never account for chromosome recoveries in excess of 50%, gametic

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lethality has been suggested as the likely mechanism.

Recent work with *In(1)sc^{4L}sc^{8R}* has identified the failure of *X:Y* pairing as the cause of the subsequent sperm inviability. A survey of a large number of *X* heterochromatic deficiencies failed to uncover any that exhibited nondisjunction without drive or vice versa (McKee and Lindsley 1987). The level of drive was found to vary greatly among the mutant deficiencies and to correlate strongly with nondisjunction level. This would seem on the face of it to lead to different explanations for the meiotic drive in the *In(1)sc^{4L}sc^{8R}* and *T(1;4)B^{S}* cases since pairing failure is not a part of the *T(1;4)B^{S}* phenotype. Yet several striking parallels between *In(1)sc^{4L}sc^{8R}* and *T(1;4)B^{S}* warrant a second look. (1) As noted above, in both cases recovery of the normal *Y* is depressed relative to the rearranged *X*. (2) In both cases it is the *larger* member of an asymmetric bivalent (the *Y* in *In(1)sc^{4L}sc^{8R}:Y*, the *Y* in *X^{P}4^{D}:Y*, and *4^{P}X^{D}* in *4^{P}X^{D}:4*) that exhibits depressed recovery. This relationship holds as well when a third sex chromosome is added to the genotype. In *In(1)sc^{4L}sc^{8R}/Y/Dp(1;f)3* males, the *Y* always pairs with the smaller free duplication yet is recovered in many fewer sperm. Similarly in *In(1)sc^{4L}sc^{8R}/YS/YL* males the *Y* fragments disjoin regularly and the longer *YL* exhibits depressed recovery (McKee 1984). (3) Chromosome recoveries are multiplicative in both cases. In *T(1;4)B^{S}* this can be calculated straight from the data as there are four observations (the frequencies of the four sperm classes) and only two parameters (the recovery of *Y* relative to *X^{P}4^{D}* and the recovery of *4^{P}X^{D}* relative to 4, leaving one degree of freedom for a test of independence (Novitski and Sandler 1957; Kastenbaum 1958). In *In(1)sc^{4L}sc^{8R}/Y* males the occurrence of nondisjunction adds a third parameter. However, when nondisjunction is estimated independently by cytological observation, the multiplicative relationship is seen to hold (McKee and Lindsley 1987). A similar test can also be done for *In(1)sc^{4L}sc^{8R}/Y/Dp* individuals, in which the *Y* and *Dp* disjoin regularly and *In(1)sc^{4L}sc^{8R}* moves at random to either pole. The two recovery parameters (*Y* relative to *Dp* and *In(1)sc^{4L}sc^{8R}* relative to nothing) prove to be independent (McKee 1984).

These parallels argue for a common explanation. While the irregularity of *X:Y* pairing in *In(1)sc^{4L}sc^{8R}* males contrasts with regular pairing in *T(1;4)B^{S}* males, this is less a problem than it first appears. Addition of *Dp(1;f)3* to *In(1)sc^{4L}sc^{8R}/Y* males produces a genotype that resembles that of *T(1;4)B^{S}*. In both cases the *X* is broken in the proximal half. Neither genotype is missing *X* material. In both genotypes the proximal portion of the *X* pairs regularly with the *Y*. The distal portion of the *X* behaves either as a univalent (*In(1)sc^{4L}sc^{8R}*) or pairs with the normal fourth (*4^{P}X^{D}*). The salient differences between the genotypes are the somewhat different locations of the *X* chromosome breakpoint (16A in *T(1;4)B^{S}*, 20 in *In(1)sc^{4L}sc^{8R}*) and the involvement of the 4th chromosome in *T(1;4)B^{S}*. The essential similarity between the genotypes is the separation of the proximal portion of the *X* including the pairing sites from the bulk of the *X* euchromatin. As noted above, both genotypes exhibit meiotic drive characterized by the same rules of size dependent and multiplicative chromosome recoveries. This phenotype must result not from a failure of *X:Y* pairing per se (since pairing is regular in both genotypes) but from a failure of the euchromatic portion of the *X* to be involved in that pairing event.

Three experiments concerning drive in *X-4* translocations are reported below. The first examines the recovery of an independently assorting 2nd chromosome free duplication in a *T(1;4)B^{S}* males. This is a test of the interpretation advanced above, namely that the *T(1;4)B^{S}* and *In(1)sc^{4L}sc^{8R}* drive systems are the same. *In(1)sc^{4L}sc^{8R}* has previously been shown to induce depressed recovery of independently assorting chromosomes (McKee 1984). The second investigates the effect of *Y*-derived pairing sites recombined onto the tip of the *4^{P}X^{D}* portion of *T(1;4)B^{S}*. This tests the hypothesis that drive is caused by failure of the *X* euchromatin to participate in *X:Y* pairing. The third is a survey of several *X-4* translocations. It examines the relation between location of *X* chromosome breakpoint and the occurrence of meiotic drive.

MATERIALS AND METHODS

The translocations used in this study are described in Lindsley and Grell (1968). Stocks carrying translocations and other chromosomes were obtained from the Bowling Green Stock Center. *Dp(2;f)f29* was kindly supplied by J. Brittnacher. Single pair crosses were made in shell vials using cornmeal-molasses agar medium and incubated at 25°. Pairs were transferred to fresh medium on day 5. Progeny in the first vial were counted on days 12, 15 and 17. Progeny in the transfer vial were counted on days 18, 20 and 23.

Crosses in Table 1 were compared by calculating R_{Dp}, the recovery probability of *Dp(2;f)f29*. This is simply the ratio of *Dp* to non-*Dp* offspring divided by the corresponding ratio in wild-type *X* controls. R_{Dp} is calculated separately for males and females since the viability of the *Dp* differs between the two sexes.

For data in Table 2, the maximum likelihood method of Kastenbaum (1958) was used to estimate sperm frequencies and standard errors. The formulas and derivations can be found in Kastenbaum.

RESULTS

Effect of *T(1;4)B^{S}* on recovery of independently assorting chromosomes: A striking property of the meiotic drive induced by *In(1)sc^{4L}sc^{8R}* and other *X* heterochromatic deficiencies is that it affects independently assorting chromosome pairs. This goes unnoticed as long as other bivalents are symmetric. But when asymmetries affecting the chromosome pairs are

TABLE 1

Recovery of *Dp(2;f)f29* in *T(X;4)* Males

Rearrangement; X breakpoint	Females		Males		R_{Dp}	
	non-*Dp*	*Dp*	non-*Dp*	*Dp*	Females	Males
Control	669	634	686	494		
T(1;4)B^S;16A	1364	691	1655	837	0.535[a]	0.702[a]
T(1;4)lv-11;15A	1438	781	1515	833	0.573[a]	0.764[a]
T(1;4)Sidky;13C	—[b]	—[b]	1495	900		0.836[a]
T(1;4)e15;13C	—[b]	—[b]	1039	753		0.987
T(1;4)A17;8B	—[b]	—[b]	322	277		1.19
T(1;4)4C3;4C	—[b]	—[b]	999	755		1.05

[a] Significantly different from 1.

[b] Daughters were not scored for these four translocations because both *Dp(2;f)f29* and the translocations carry y^+.

introduced into an Xh^- genotype, they lead to skewed chromosome recoveries. For example males heterozygous for *T(2:3)bw^{v4}* generate reciprocal sperm classes duplicated for most of 3L and deficient for 3L by adjacent segregation. In Xh^+ males these two sperm classes are recovered in equal porportions. In Xh^- males, however, the 3L-deficient classes are recovered in considerable excess.

Similarly, otherwise normal males which carry the heterochromatic autosomal free duplication (*Dp-(2;f)f29*) in addition to two normal second (*2*) chromosomes produce equal number of *2* + *Dp*-bearing and *2*-bearing sperm. However in the presence of *In(1)sc^{4L}sc^{8R}* or other *X* heterochromatic deficiencies, recovery of *2* + *Dp*-bearing sperm is substantially depressed relative to *2*-bearing sperm (McKee 1984).

If, as suggested above, *X* heterochromatic deficiencies and *X-4* translocations cause drive for the same reason, then *T(1;4)B^S* should interact with autosomal asymmetries in the same way. To test this, males of the genotypes *T(1;4)B^S/Y; 2/2/Dp* and *y/Y; 2/2/Dp* were constructed and crossed to *y w/y w* females. The results in Table 1, lines 1 and 2, indicate that *T(1;4)B^S*, like *In(1)sc^{4L}sc^{8R}*, substantially reduces recovery of the independently assorting autosomal free duplication. In both sexes, recovery of *Dp(2;f)f29* is substantially lower in *T(1;4)B^S* than in the control males.

Effect of pairing sites linked to the *4^{P}X^D* Half of *T(1;4)B^S* on drive: The hypothesis outlined above, that the separation of the distal euchromatic portion of the *X* from the heterochromatic pairing sites is responsible for drive both in *T(1;4)B^S* and *In(1)sc^{4L}sc^{8R}* males, is susceptible to test. Pairing sites and other heterochromatic material were added to the *4^{P}X^D* portion without otherwise altering the *T(1;4)B^S* genotype. This was done by generating females heterozygous for *T(1;4)B^S* and *YSX·*(=FR1), an attached-*XY* chromosome in which the short arm of the *Y* (where the main *Y* pairing sites are located) is appended to the tip of the *X*. A single crossover carrying the tip of *YSX·* and the base of *T(1;4)B^S* was recovered. This is called *YSX·,T(1;4)B^S*. Males of the genotype *YSX·, T(1;4)B^S/y$^+$Y* were bred. These males have three chromosomes with pairing site material: *y$^+$Y*, *X^{P}4^D*, and *4^{P}YSX·^{D}*. By analogy with other three sex-chromosome genotypes in Drosophila males, these chromosomes would be expected to form a trivalent at meiosis I. If the pairing-drive hypothesis is correct, the four disjunctional classes should be recovered in normal (nondrive) ratios.

The males were crossed to two different types of females: *C(1)DX/Y* (cross 1) and *C(1)DX/X^{P}4^D* (cross 2), following the procedure worked out by Novitski and Sandler (1957). In the former cross *4^{P}X^D;X^{P}4^D* sperm, *4;Y* sperm, and *X^{P}4^D;4* sperm are recovered; *Y;4^{P}X^D* sperm are not. In the latter cross, *4^{P}X^D;Y* sperm, *4;Y* sperm, and *X^{P}4^D;4* sperm are recovered but *4^{P}X^D;X^{P}4^D* sperm are not. The frequencies of the four sperm classes can be estimated using the data from both crosses and the method of maximum likelihood. The maximum likelihood solutions were worked out by Kastenbaum (1958). The results and the maximum likelihood estimates are displayed in Table 2 for both genotypes.

In addition to the sperm frequency estimates, a drive parameter (*Z*) based solely on euploid progeny is calculated for all experiments in Table 2. Its use is motivated by the fact that sperm frequency estimates are biased by zygotic inviability of aneuploid classes in some of the translocations. *Z* is basically a ratio of the *4^{P}X^D;Y* class from cross 2 to the *4^{P}X^D;X^{P}4^D* class from cross 1 and thus reflects the sensitivity difference between the *Y* and the *X^{P}4^D* translocation half. In order to correct for the fact that the two classes come from different experiments and therefore different size sperm samples, each is first divided by the *Y;4* class from the same cross. Thus *Z* = *4^{P}X^D;Y/4;Y* from cross 2 divided by *X^{P}4^D;4^{P}X^D/4;Y* from cross 1.

Both the sperm frequency estimates and the *Z* values indicate that the addition of heterochromatin which contains pairing sites to the tip of the distal half of *T(1;4)B^S* substantially reduces drive relative to *T(1;4)B^S* controls. In fact recoveries of reciprocal sperm classes (*X^{P}4^D;4^{P}X^D* vs. *Y;4* in cross 1 and *4^{P}X^D;Y* vs. *X^{P}4^D;4* in cross 2) are not significantly different from equality in the *YSX·,T(1;4)B^S* cross.

***X* chromosome breakpoint and meiotic drive in *T(1;4)* translocations:** Since the foregoing implies that separation of distal *X* material from the pairing sites is the crucial factor in meiotic drive, it is a matter of some interest to determine the location of the distal material that must be attached to the pairing sites. Two general possibilities suggest themselves. There could be a single gene or group of genes that must participate in *X:Y* pairing in order to carry out its spermatogenic function(s). Alternatively, perhaps all *X* genes must be linked to pairing sites in order to accomplish a pairing-dependent chromsome-level

TABLE 2

***T(X;4)* males crossed to *C(1)DX/Y* and *C(1)DX/X^P-4^D* females**

Male genotype	Female genotype	Sperm genotype				N	Z^a
		$X^P4^D;4^PX^D$	$Y;4$	$4^PX^D;Y$	$X^P4^D;4$		
$T(1;4)B^S/y^+Y$	(1) $C(1)DX/Y$	1310	737	†	1236	3283	0.497
	(2) $C(1)DX/X^P4^D$	†	495	437	728	1660	
Sperm Class Frequencies		0.328 ($\pm 8.50 \times 10^{-3}$)	0.191 ($\pm 5.16 \times 10^{-3}$)	0.177 ($\pm 8.37 \times 10^{-3}$)	0.304 ($\pm 6.31 \times 10^{-3}$)		
$YSX\cdot,T(1;4)B^S/y^+Y$	(1) $C(1)DX/Y$	527	478	†	473	1478	0.780
	(2) $C(1)DX/X^P4^D$	†	687	591	606	1884	
Sperm Class Frequencies		0.276 ($\pm 1.12 \times 10^{-2}$)	0.258 ($\pm 7.13 \times 10^{-3}$)	0.227 ($\pm 9.35 \times 10^{-3}$)	0.239 ($\pm 6.90 \times 10^{-3}$)		
$T(1;4)e15/B^SY$	(1) $C(1)DX/Y$	1849	1406	†	791	4046	1.036
	(2) $C(1)DX/X^P4^D$	†	309	421	113	843	
Sperm Class Frequencies		0.296 ($\pm 9.74 \times 10^{-3}$)	0.231 ($\pm 6.82 \times 10^{-3}$)	0.351 ($\pm 1.60 \times 10^{-2}$)	0.122 ($\pm 4.54 \times 10^{-3}$)		
$T(1;4)lv\text{-}11/y^+Y$	(1) $C(1)DX/Y$	402	196	†	441	1039	0.501
	(2) $C(1)DX/X^P4^D$	†	36	37	52	125	
Sperm Class Frequencies		0.308 ($\pm 1.83 \times 10^{-2}$)	0.156 ($\pm 1.09 \times 10^{-2}$)	0.205 ($\pm 3.22 \times 10^{-2}$)	0.331 ($\pm 1.70 \times 10^{-2}$)		

$^a Z = \dfrac{4^PX^D;Y/Y;4(2)}{X^P4^D;4^PX^D/Y;4(1)}$.

event. Perhaps sex chromosome condensation begins at the pairing sites and spreads distally. These two alternatives can be distinguished by surveying meiotic drive in *X-4* translocations. The former hypothesis would suggest a sharp line of demarcation. All translocations broken proximal to the line should cause drive; all translocations broken distal to the line should behave normally. The latter hypothesis would suggest a more gradual gradient with drive levels declining as the breakpoint moves distally.

Six translocations were surveyed; their breakpoints range from 4A to 16A. Two different drive assays were performed. In one, the effect of the translocation on recovery of the independently assorting *Dp(2;f)f29* was monitored. For this purpose *T(X;4)i/Y 2/2/Dp(2;f)f29*, y^+ males were crossed to *y w/y w* females. Recovery of the *Dp* (which is marked with y^+) was monitored in sons or, for *y* or y^2 translocations, in both sons and daughters. The advantage of this assay is that it avoids the viability problems encountered in the NOVITSKI-SANDLER assay described above. It can be carried out for all translocations. For all crosses involving *Dp(2;f)f29*, the parameter R_{Dp} was calculated. This is simply the ratio of *Dp* to non-*Dp* progeny classes, divided by the corresponding ratio for wild type *X* controls. The wild type controls are important because the *Dp* does affect zygotic viability, particularly in sons. A different ratio was calculated for males and females since the viability effects are different in the two sexes.

The second assay was the NOVITSKI-SANDLER method of crossing *T(X;4)/y$^+$Y* or *B^{S}Y* males to both *C(1)DX/Y* and *C(1)DX/X^{P}4^D* females, as described above. Since the method depends upon viability and fertility of *C(1)DX/X^{P}4^D* females, it is usable only for translocations with proximal *X* breakpoints. The data are reported in Table 2, along with maximum likelihood estimates of the sperm classes (KASTENBAUM 1959). These estimates are meaningful for the translocations with *X* chromosome breakpoints proximal to 13C since only for these translocations do all sperm generate a fully viable progeny class. For these translocations, drive is reflected in substantial deviations from the expected 25% for each sperm class. For the 13C translocation tested, the *C(1)DX/X^{P}4^D* progeny class is semilethal due to hyperploidy. This renders estimates of sperm frequencies from aneuploid classes ambiguous. Use of the drive parameter *Z*, described earlier, facilitates comparison of translocations as it uses only the data for the euploid classes.

Both the *Dp(2;f)f29* and NOVITSKI-SANDLER assays were used for three of the translocations: *T(1;4)B^S*, *T(1;4)lv-11*, and *T(1;4)e15*. Both gave the same results for all three. *T(1;4)B^S* and *T(1;4)lv-11* show drive; *T(1;4)e15* does not. Thus the two assays agree and can be used interchangeably.

The results indicate a dividing line around 13. One of the two 13C translocations (*T(1;4)e15*) shows no drive, the other(*T(1;4)*Sidky) very mild drive. Translocations broken distal to 13C are wild type; those broken proximal to 13C cause drive. Among the "mutant" translocations in Table 2, there is a clear gradient and it correlates with breakpoint. The more proximal the break, the stronger the drive. Thus elements of both hypotheses are confirmed. There is a dividing line but also a gradient. This could reflect a threshold situation in which abnormalities appear only when a minimum amount of *X* material is separated from pairing sites. Alternatively, some uniquely important material could be located in the 13C–16A region.

DISCUSSION

No substantial barriers to a common interpretation of the *In(1)sc^{4L}sc^{8R}* and *T(X;4)B^S* meiotic drive cases remain. In both cases drive is caused by separation of distal *X* material from *X* pairing sites. In both cases the results are skewed recovery ratios in which small chromosomes are recovered better than large ones and sperm recovery probabilities are inversely proportional to chromatin content. The experiments concerning position of *X* breakpoint imply that the amount of *X* material separated from pairing sites may be the causal factor. Unfortunately, it is not easy to reconcile attached-*XY*/*Dp* drive with this interpretation. Males carrying an attached-*XY* chromosome and a heterochromatic free *X* duplication can (depending on the *Dp*) show rather extreme drive. As in the other systems, drive favors the smaller *Dp* over the larger attached-*XY*. But there need not be any pairing failure (many drive-inducing *Dp*s pair regularly with the attached-*XY*). And there is no *X* chromosome discontinuity. The implication is that drive can also be caused by something other than separation of *X* euchromatin from pairing sites.

An adequate explanation of meiotic drive in *In(1)sc^{4L}sc^{8R}* and *T(1;4)B^S* males must reconcile the cis and trans aspects of this phenomenon. Drive is caused by separation of *X* material from meiotic pairing sites. This is the cis aspect. It is tempting to speculate that meiotic gene inactivation and the subsequent chromatin conformational changes necessary for normal sperm function are initiated at meiotic pairing sites. For sex chromosomes these changes must then spread the length of the chromosome. Sex chromosome discontinuities lower the likelihood of successful spreading. Autosomes do not face the same problem since autosomal pairing sites are not localized to the heterochromatin but distributed throughout the chromosomes (YAMAMOTO 1979; HILLIKER, HOLM and APPELS 1982). The consequences of sex chromosomal pairing abnormalities are not limited to sex chromosomes however, but affect all chromosomes in proportion to size. This is the trans aspect. It rules out all models in which chromosomes that fail to pair become sperm-lethals. Instead it points to a physiological abnormality in the developing cyst that impinges upon all sperm. The nature of this abnormality and its relationship to meiotic pairing remain mysterious.

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