LETTER TO THE EDITOR

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Brain benzodiazepine receptor changes during ageing

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The medical and social relevance of the side effects induced in the elderly by benzodiazepines imposes various pharmacological problems. In particular it has been hypothesized that they are related with the possible pharmacokinetic and pharmacodynamic changes which, in the aged people, produce unwanted reactions such as drowsiness and unsteadiness of gait (Saltzman et al 1975).

We report that beside the possible pharmacokinetic differences which characterize the ageing process, some changes may be detected also at the level of specific brain receptors with which benzodiazepines interact. The presence of specific benzodiazepine receptors in various human and animal brain areas is now well established (Braestrup & Squires 1977; Braestrup et al 1977).

However, various neurotransmitter receptors are significantly affected by ageing. Greenberg & Weiss (1979) reported the reduced capacity of central β-adrenoceptors to develop supersensitivity after decreased neuronal input, while Govoni et al (1980) found a diminished number of dopamine receptors in aged rats.

Mature (3–4 months) and aged (24–28 months) male Sprague-Dawley rats were housed at constant temperature and humidity with free access to food and water. [^{3}H]Diazepam specific binding was measured according to Braestrup & Squires (1977). To avoid the possibility of endogenous GABA affecting [^{3}H]diazepam binding, the freshly prepared membranes were extensively washed. A Scatchard analysis was made.

We measured [^{3}H]diazepam specific binding in various brain regions of old rats. There were no changes in cortex (853 ± 7 and 832 ± 6·8 fmol/mg^{-1} prot. mean with s.e.), corpus striatum (462 ± 6·2 and 438 ± 6·3 fmol mg^{-1} prot.), cerebellum (750 ± 6·8 and 773 ± 6·4 fmol mg^{-1} prot.) and hypothalamus (537 ± 7·3 and 545 ± 7 fmol mg^{-1} prot.) of mature and old rats respectively. Only in the hippocampus of mature and old rats were we able to detect a significant increase of [^{3}H]-diazepam specific binding. The kinetic values of this study are reported in Table 1, which shows an increase in the total number of active sites (B_{max}) in the aged rats for benzodiazepines in the hippocampus without relevant changes in the affinity constant (K_D) of the receptors.

These results imply an increase of the specific receptor proteins for benzodiazepines or the unmasking of spare receptors during ageing. As clinical data indicate a change in some benzodiazepine effects during ageing (Epstain 1978), it may be hypothesized that changes in the response to these drugs may be ascribed to age-induced modifications of the synaptic transmission in limbic areas.

Table 1. Characteristics of [^{3}H]diazepam, specific binding in hippocampus of aged and mature rats.

	[^{3}H]Diazepam specific binding	
	K_D	B_{max}
mature (3–4 months)	1·9 ± 0·2	135 ± 7
aged (26–28 months)	1·5 ± 0·2	189 ± 8*

* $P < 0·1$ in respect to mature values.

K_D values are expressed as nM, B_{max} are expressed as fmol mg^{-1} protein.

Values are the mean ± s.e. of five determinations using six concentrations of radioligand.

The experiments have been performed as previously indicated.

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