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Study: Inflammation in the brain enhances the side-effects of hypnotic medication

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In a study recently published in the *European Journal of Pharmacology researchers* at Okayama University show how the presence of inflammation in the brain can increase its sensitivity to benzodiazepines.

Benzodiazepines (BZDs) are drugs commonly prescribed for anxiety, insomnia and seizures. However, in post-surgical patients taking BZDs, undue side-effects such as excessive sleepiness, weakness and delirium have often been observed. Associate Professor Yoshihisa Kitamura and Professor Toshiaki Sendo from Okayama University and colleagues have recently shown that inflammation, which is a normal after-effect of surgery, might be potentiating the effects of these drugs.

BZDs act by activating a receptor in the brain known as the $GABA_A$ receptor ($GABA_R$). Typically, $GABA_R$ is activated by chemicals inherently present in the brain. However, because drugs like BZDs can mimic these chemicals, they are used to stimulate the activity of $GABA_R$ in the lab. When $GABA_R$ is excessively activated, animals tend to exhibit inhibitory effects, such as loss of consciousness and loss of normal reflexes. One such reflex observed in animals is the righting reflex, that is, their tendency to immediately prop back up on their paws, when made to lay supine. This suggests that the animal is awake and alert.

For their study, the investigators first artificially stimulated $GABA_R$ in the brains of mice, using a sedative called pentobarbital. As expected, pentobarbital induced a loss of the righting reflex (LORR). Under normal conditions, BZDs should prolong the duration of the LORR, as they activate $GABA_R$ even further.

This was observed with a high, but not low, dose of the BZD, diazepam. Another group of mice was then treated with a bacterial endotoxin that triggered inflammation in their brains. When this group was given diazepam, it prolonged the duration of LORR even at a low dose, suggesting sensitivity to diazepam in the inflammation-induced mice.

To address if these effects were specific to $GABA_R$, a drug that inactivates these receptors was subsequently used. The duration of LORR in these mice was considerably reduced, confirming the role of $GABA_R$. Interestingly, even when the mice were given a drug that reduces inflammation, the duration of LORR was reduced. Inflammation was indeed the culprit. The prolongation of reflex loss seen in mice given diazepam was thus linked directly to $GABA_R$ and inflammation in the brain.

Associate Professor Yoshihisa Kitamura and and Professor Toshiaki Sendo from Okayama University and colleagues speculate that inflammation might result in an increase in the number of $GABA_R$ in the brain, which makes the inhibitory effects of diazepam more profound. “Thus, inhibition of inflammation in the brain may be a promising strategy to prevent the effects of benzodiazepines, such as weakness, over-sedation, and delirium, experienced in patients after surgery”, concludes his team. Prescribing anti-inflammatory drugs to these patients could, perhaps, be one such strategy.