

ESSAY 1

Answers must be written out in paragraph form. Outline form is not acceptable. Labeled diagrams may be used to supplement discussion, but a diagram without a written explanation will not receive credit. You must cite the source of all outside information you include. Include the page number of information from the course textbook or the web address of information found online.

Polymorphisms of the *catechol-O-methyltransferase* (*COMT*) gene (Figure 1) have been associated with alcoholism. *COMT* is an enzyme that regulates the levels of signaling molecules (hormones and neurotransmitters) in the body. The *COMT* gene encodes two isoforms of the enzyme: a soluble form (S-COMT) found in the cytoplasm of cells of the liver, kidneys, and blood, and a membrane-bound form (MB-COMT) produced primarily by nerve cells (neurons) of the brain.

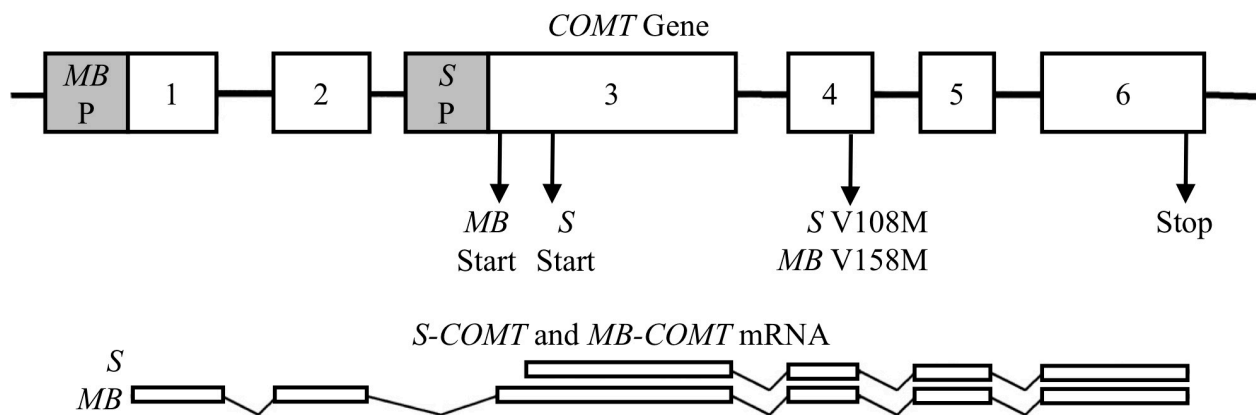


Figure 1. Structure of the *COMT* gene and *S-COMT* and *MB-COMT* mRNA (Sasaki, Kaneuchi, Sakuragi, & Dahiya, 2003). The six exons (numbered rectangular boxes), the introns (thin lines between the boxes), locations of the *MB-COMT* and *S-COMT* promoters (*MB P* and *S P*), translation start and stop codons, and the exons remaining in each mature transcript (rectangular boxes in the mRNA) are represented. The location of a common valine-to-methionine substitution at positions 108 and 158 of the *S-COMT* and *MB-COMT* polypeptides, respectively (Craddock, Owen, & O'Donovan, 2006), is indicated (*S V108M* and *MB V158M*).

- (a)
- (i) **Explain** how a single *COMT* gene can encode both the *S-COMT* and *MB-COMT* polypeptides.
 - (ii) **Describe** ONE evolutionary advantage of a single gene encoding multiple polypeptides.

In an effort to better understand the relationship between the *COMT* gene and alcoholic behavior, researchers compared *COMT* expression in different regions of the brains of male and female rats selectively bred for free-choice alcohol preference (P rats) and alcohol-naïve Wistar rats (McCane et al., 2018). Subjects were separated into groups by sex and strain (P or Wistar) and given a choice between two water bottles: one containing water and the other containing 20% ethanol (alcohol). After 24 hours of access to the two bottles, bottles were removed, fluid intake was measured, and bottles were replaced. Animals were weighed immediately before each bottle placement to calculate ethanol intake per kilogram of body mass (Figure 2). Following behavioral testing, subjects were euthanized and their brains were extracted for dissection. A western blot analysis was used to assess the *COMT* protein levels in three regions of the brain known to be involved in drug seeking behavior: the prefrontal cortex (PFC), hippocampus (HC), and striatum (Figure 3).

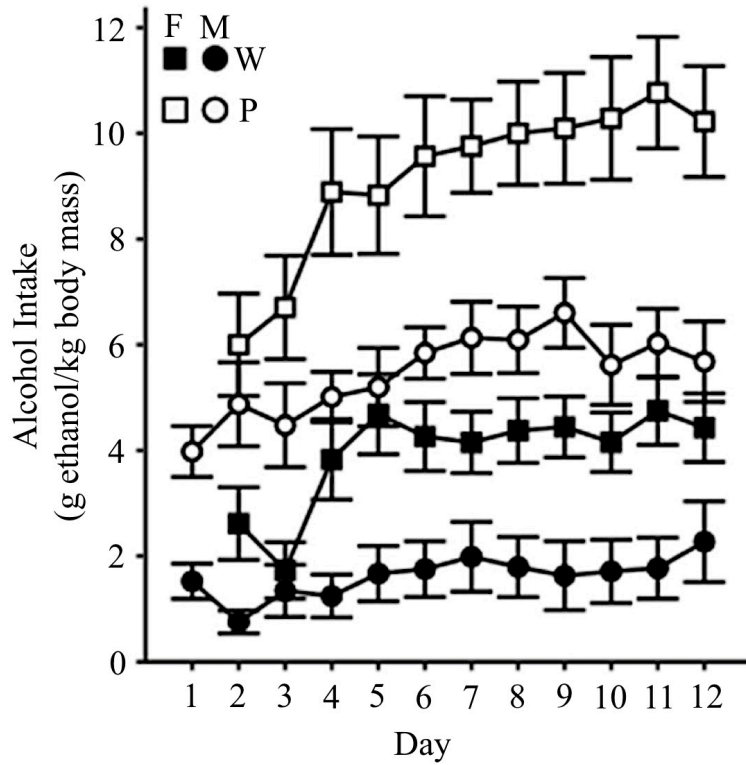


Figure 2. Ethanol intake for female (square) and male (circle) P (open) and Wistar (closed) rats. Error bars represent $\pm 2SE_{\bar{X}}$.

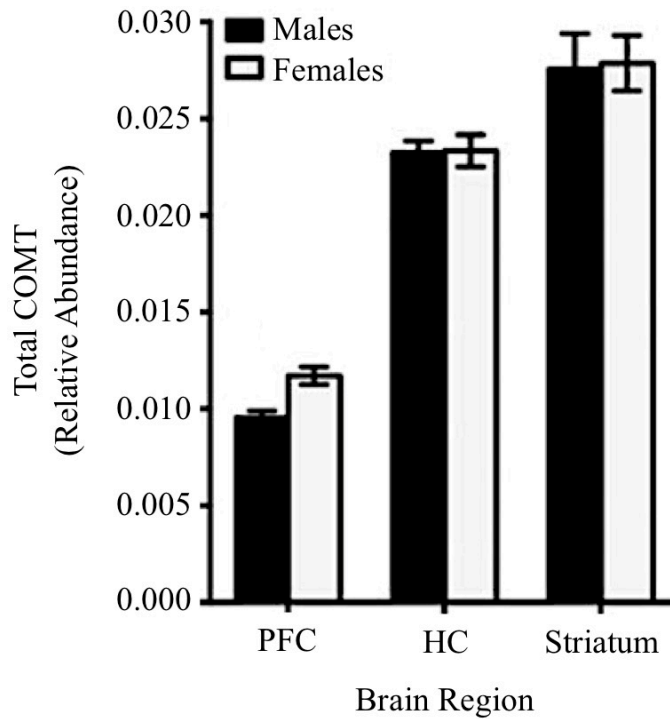


Figure 3. Relative abundance of COMT in different brain regions of male and female P rats. Error bars represent $\pm 2SE_{\bar{X}}$.

- (b)
- Give ONE reason** why it may be invalid to make inferences about the role of *COMT* expression in increased ethanol intake based on a comparison of *COMT* protein levels in P and Wistar rats.
 - Propose a replacement** for one of the treatment groups in the original experimental design that would produce results that could be used to evaluate the claim that decreased *COMT* expression causes increased alcohol intake in rats.
 - Pose an ethical question** that the Institutional Review Board (IRB) most likely considered before approving the use of rats in this experiment.
- (c)
- Describe** the differences in alcohol consumption between male and female P rats.
 - Identify** the region of the brain most likely responsible for these differences.
 - Use [Figure 3](#) to **provide support** for your identification.

In the brain, MB-COMT contributes to the degradation of dopamine (Figure 4), a neurotransmitter associated with reward-motivated behaviors, including addiction.

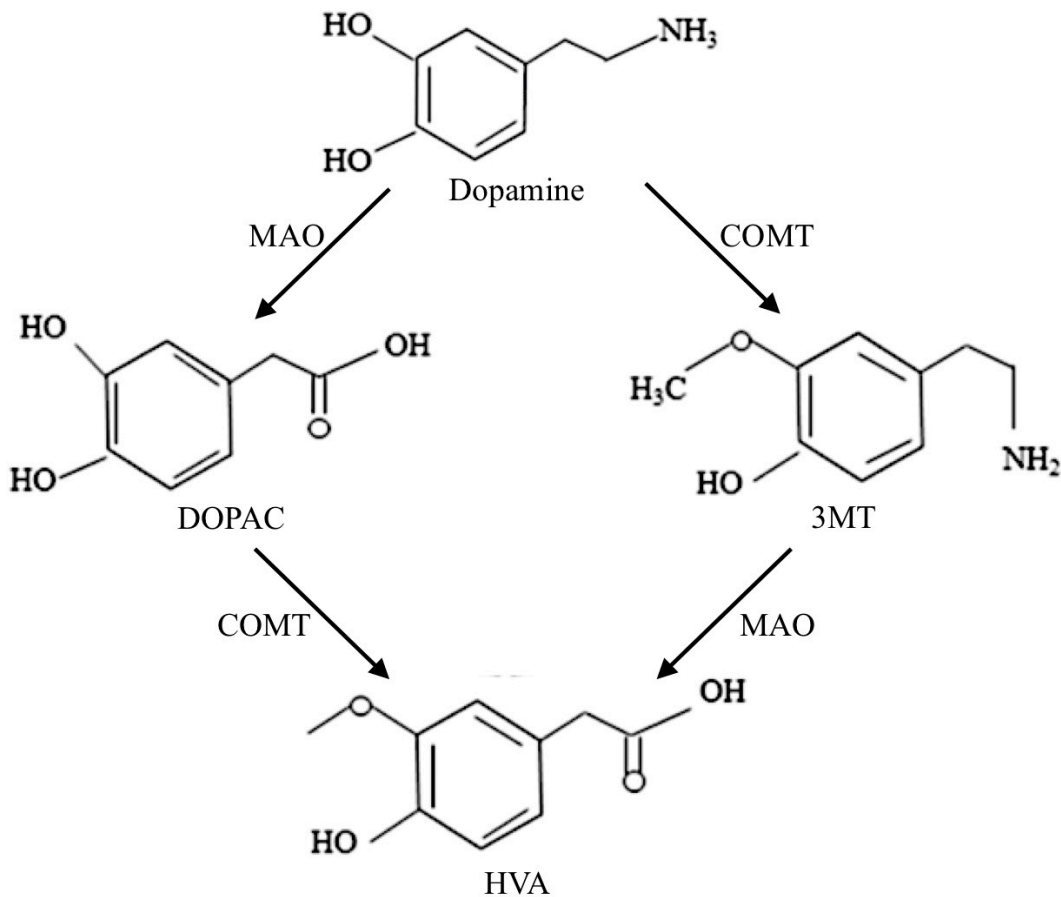


Figure 4. Model of the dopamine degradation pathway (Taj & Jamil, 2018). The enzymes catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO) catalyze the breakdown of dopamine into intermediates, 3,4-dihydroxyphenyl acetic acid (DOPAC) and 3-methoxytyramine (3MT), and ultimately into homovanillic acid (HVA).

(d)

- (i) **Provide reasoning** to support the claim that a mutation in the *MB-COMT* promoter can result in a reduction in MB-COMT polypeptide levels.
- (ii) Based on an analysis of Figure 4, **predict** the effect of decreased *COMT* expression on the level of DOPAC and on the level of 3MT in a neuron in the brain.
- (iii) **Justify** each prediction.

References

- Craddock, N., Owen, M.J., & O'Donovan, M.C. (2006). The *catechol-O-methyl transferase (COMT)* gene as a candidate for psychiatric phenotypes: Evidence and lessons. *Molecular Psychiatry*, 11(5), 446–458.
- McCane, A. M., DeLory, M. J., Timm, M. M., Janetsian-Fritz, S. S., Lapish, C. C., & Czachowski, C. L. (2018). Differential COMT expression and behavioral effects of COMT inhibition in male and female Wistar and alcohol preferring rats. *Alcohol*, 67, 15–22.
- Sasaki, M., Kaneuchi, M., Sakuragi, N., & Dahiya, R. (2003). Multiple promoters of *catechol-O-methyltransferase* gene are selectively inactivated by CpG hypermethylation in endometrial cancer. *Cancer Research*, 63(12), 3101–3106.
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