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.

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 (SV108M and MB V158M).

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. In the brain, MB-COMT contributes to the degradation of dopamine (Figure 2), a neurotransmitter associated with reward-motivated behaviors, including addiction.
Figure 2. 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-dihydroxyphenol acetic acid (DOPAC) and 3-methoxytyramine (3MT), and ultimately into homovanillic acid (HVA).

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 3). 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 4).
Figure 3. Ethanol intake for female (square) and male (circle) P (open) and Wistar (closed) rats. Error bars represent ±2SEX̄.

Figure 4. Relative abundance of COMT in different brain regions of male and female P rats. Error bars represent ±2SEX̄.
(a) **Explain** how a single COMT gene can encode both the S-COMT and MB-COMT polypeptides. **Describe** one evolutionary advantage of a single gene encoding multiple polypeptides.

(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 and **identify** the region of the brain most likely responsible for these differences. Use Figure 4 to **provide support** for your identification.

(d) **Provide reasoning** to support the claim that a mutation in the MB-COMT promoter can result in a reduction in MB-COMT polypeptide levels. Based on an analysis of Figure 2, **predict** the effect of decreased COMT expression on the level of DOPAC and on the level of 3MT in a neuron in the brain. **Justify** each prediction.

**References**


