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学 位 論 文 要 旨

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題 目：Study on the pharmacological characteristics of the avian basilar arteries
(トリ脳底動脈の薬理学的特徴に関する研究)

論文要旨：

The basilar artery courses along the ventral side of the medulla oblongata and ultimately splits into the posterior cerebral arteries. These arteries establish connections to the internal carotid arteries via posterior communicating arteries and provide oxygenated blood to the cerebellum, brain stem, and occipital lobes. Investigating the basilar artery is significant as it constitutes one of the primary resistance vessels in the brain. The physiological responses of the basilar artery appear to influence not only cerebral blood flow (CBF) but also local microvascular pressure. The unique features of the cerebral circulation make it difficult to extrapolate findings from peripheral blood vessels. The cerebral arteries are more productive and greatly influenced by vasoactive substances than others which make them vulnerable to pathological condition. Endogenous factors with strong vasoregulatory properties produced either locally or carried by blood to the basilar artery have been implicated in the local control of CBF. The process is intricate, involving various factors, including local-chemical and endothelial factors, autacoids, and innervation systems, working together to safeguard optimal blood flow to the brain under diverse physiological and pathological conditions. Our research focuses on the responsiveness of basilar artery induced by those receptor-mediated stimuli, such as 5-Hydroxytryptamine (5-HT), noradrenaline (NA), acetylcholine (ACh), histamine (His), angiotensin (Ang) II, and bradykinin (BK). And such these researches could be investigated by organ bath system, allowing for a comprehensive examination of vascular reactions under controlled experimental conditions.

In the first chapter, the adrenergic receptor subtypes of chicken basilar arteries (CBAs) were characterized. The response of these arteries to noradrenaline (NA) was evaluated, induced contraction of arteries in resting tension, but induced relaxation of arteries in 5-hydroxytryptamine (5-HT) pre-contraction. Furthermore, the use of propranolol (a β-AR antagonist) and phentolamine (a α-AR antagonist) respectively enhanced those contraction and relaxation, to reveal the presence of both alpha and beta (α and β) receptors. Concentration-dependent relaxations induced by a range of β-AR agonists provided insights into their relative potency. Notably, isoproterenol demonstrated the highest potency, followed by noradrenaline, adrenaline, and procaterol.

To further explore the β-AR subtypes, several β-AR antagonists were employed, including propranolol for $\beta_{1,2,3}$-ARs, atenolol for β_1-ARs, butoxamine for β_2-ARs, and SR 59230A for β_3-ARs. In the Schild regression analysis, Propranolol was the only antagonist to yield a slope diverging from unity, suggesting the presence of multiple β-AR subtypes. Our Schild regression analysis for atenolol and butoxamine also indicated that neither β_1-AR nor β_2-AR was the dominant subtype with their low pA_2 value of 5.95 and 5.14, respectively. On the contrary, SR 59230A exhibited a pA_2 value (7.52) close to that reported for the relevant receptor subtype. Moreover, the treatment of N^{ω}-nitro-L-arginine (L-NNA, a nitric oxide synthase (NOS) inhibitor) was found to inhibit SR 58611A (a β_3-AR agonist)-induced relaxation, suggesting the involvement of endothelial NOS in β_3-ARs mediated vasodilation. Additionally, experiments involving basilar arterial strips containing endothelium demonstrated that SR 58611A treatment induced nitric oxide production, which was decreased by L-NNA, further suggesting β_3-ARs mediated vasodilation via the NOS pathway.

In the second chapter, I investigated the responsiveness of duck basilar arteries (DBAs) to various vasoactive substances, encompassing 5-HT, histamine (His), angiotensin (Ang) II, NA, acetylcholine (ACh), and avian bradykinin ornithokinin (OK). This study aimed to characterize the receptor subtypes involved in arterial contraction and relaxation, as well as to examine the role of endothelial NO in vitro.

In our first result, L-NNA-induced contraction under resting tension and indomethacin-induced relaxation under contraction induced with L-NNA, suggesting the spontaneous NO and spontaneous thromboxane A_2 are released from endothelial cells of DBAs. However, a key difference was that the L-NNA-induced contraction in ducks (30.5%) was markedly weaker than that in chickens (122.1%), suggesting that ducks experience less involvement of spontaneous endothelial NO than chickens.

Furthermore, our results indicated that arterial contraction in duck basilar arteries was primarily mediated by 5-HT_1 and H_1 receptors, whereas relaxation was elicited by β_3-adrenergic and M_3 receptors. Notably, OK induced a biphasic response in duck basilar arteries, while Ang II had no discernible effect. The involvement of endothelial NO was assessed, revealing its critical role in relaxation mediated by M_3 and OK receptors. However, in contrast to chicken basilar arteries, β_3-ARs and His receptors in duck basilar arteries did not appear to contribute significantly to endothelial NO-mediated relaxation.

In conclusion, these two studies provide valuable insights into the receptor subtypes and endothelial function in avian basilar arteries. We suggest that CBA exhibit a significant contribution of β_3-ARs, especially on the endothelium, in vasodilation through NO release. In contrast, DBA is characterized by a smaller endothelial release of NO and a smaller degree of endothelial involvement in its reactivity than the BA of the chicken. NO plays a role with M_3 but not β_3-adrenergic receptors. These physiological differences may help explain varying susceptibility to diseases such as highly pathogenic avian influenza between poultry species. Further research is warranted to explore the underlying mechanisms and therapeutic implications of these findings.