WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 8, Issue 4, 716-722. Research Article ISSN 2277– 7105

STUDY OF NEUROTRANSMITTERS IN PULMONARY TUBERCULOSIS

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Article Received on
24 Jan. 2019,

Revised on 14 Feb. 2019,
Accepted on 07 March 2019

DOI: 10.20959/wjpr20194-14493

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ABSTRACT

Background: Isoniazid is a "first line" drug for treatment of pulmonary tuberculosis (*Mycobacterium tuberculosis*) which inhibits the synthesis of mycolic acid in the mycobacterial cell wall. Isoniazid has significant effect on several biochemical pathways, including the metabolism of pyridoxine (vitamin B_6) substantially reducing its activity, leading to clinical pyridoxine depletion. Pyridoxine is a necessary cofactor for production of the neurotransmitter gamma-aminobutyric acid (GABA). Inactivation of pyridoxine leads to depletion of GABA. The majority of tyrosine that does not get incorporated into proteins is catabolized for energy production. One of the significant fates of tyrosine is conversion to catecholamines i.e. dopamine, norepinephrine, and epinephrine. The levels of Dopamine are also influenced by pyridoxine. Low levels of dopamine tend to result in very serious depression or anxiety in TB patients. **Methods:** Case–Control study comprised 50 control, 50 newly diagnosed TB (CAT I) and 50 TB with multidrug-resistance (MDR). Blood samples analysed for Dopamine and

GABA by Enzyme linked immunosorbant assay (ELISA), total proteins by Automated Chemistry analyser and vitamin C by HPLC. **Results:** The serum levels of Dopamine, GABA, and Total protein showed a remarkable decrease in tuberculosis patients than in control. Also, correlation studies show negative correlation among the parameters leading to increased inflammation. **Conclusion:** Protein, Vitamin C and Vitamin B_6 plays role in catecholamine metabolism of Dopamine and GABA pathway. Decrease in levels leading to increase in inflammation due to alpha-TNF and cytokines causing progression of disease.

KEYWORDS: Dopamine, GABA, Pulmonary Tuberculosis, Neurotransmitter.

INTRODUCTION

Tuberculosis (TB) is a chronic infectious disease mainly caused by *mycobacterium tuberculosis* (MTB). Isoniazid is a "first line" drug in the treatment of pulmonary and tuberculosis (*Mycobacterium tuberculosis*). It inhibits the synthesis of mycolic acid in the mycobacterial cell wall. Isoniazid is structurally related to pyridoxine. Isoniazid is an inhibitor of several cytochrome P450-mediated functions, particularly demethylation, oxidation, and hydroxylation.[1, 2]

Pyridoxine in its active form is a necessary cofactor for production of the neurotransmitter gamma-aminobutyric acid (GABA). Two mechanisms of pyridoxine inhibition were proposed: a) Isoniazid inhibits the enzyme pyridoxine phosphokinase, which converts pyridoxine to its active form, pyridoxal phosphate b) Isoniazid binds to pyridoxal phosphate, forming an inactive hydrazone complex that is excreted in the urine. Inactivation of pyridoxine leads to a depletion of GABA in the brain which increases the susceptibility to seizures. Thus, the neurotoxic effects of isoniazid are specifically counteracted by the administration of pyridoxine.[1, 2, 3]

Tyrosine is transported into catecholamine-secreting neurons and adrenal medullary cells where catechaolamine neurotransmitters are converted to dopamine, norepinephrine, and epinephrine. The first step in the process requires tyrosine hydroxylase, which requires tetrahydrobiopterin as cofactor. The dependence of tyrosine hydroxylase on H_4B necessitates the coupling to the action of dihydropteridine reductase. The hydroxylation reaction generates DOPA (3,4 dihydrophenylanine) DOPA decarboxylase converts DOPA to dopamine, dopamine β- hydroxylase converts dopamine to norepinephrine and phenylethanolamine N-methyltransferase converts norepinephrine to epinephrine. Within the substantia nigra and

some other regions of the brain, synthesis proceeds only to dopamine. Catecholamine influences many cellular activities, including behaviour, hormone synthesis and release, blood pressure and intracellular ion transport. Close interactions between dopamine and nor-epinephrine, serotonin, GABA, glutamate, acetylcholine, opiates and CCK among others; have been documented.[4] Low levels of dopamine tend to suggest low levels of norepinephrine, and the absence or near absence of these chemicals in concert could result in very serious depression or anxiety.

Despite the high burden of disease, there have been surprisingly few studies of the acute phase and plasma catecholamine/cortisol stress hormone responses in patients with active pulmonary tuberculosis. Studies have shown that prevalence of depression in tuberculosis patients was found to be 39.5%. When TB is diagnosed, patients and their families must receive counselling, nutrition, and economic support.[5, 6, 7]

MATERIAL AND METHODS

The Case–Control study comprised of 50 normal healthy human volunteers (Control), 50 newly diagnosed TB patients (CAT I) and 50 TB patients with multidrug-resistance (MDR). Recruited subjects were of both genders in age group of 18- 60 years. Blood serum samples were collected, stored at -80°C and analysed for dopamine by BA E- 5300 LDN -LDN Labor Diagnostika, NORD GMBH & Company KG, Nordhorn, Germany and GABA by CAT NO YHB1299HU, YH Biosearch Laborator by Enzyme linked immunosorbant assay (ELISA) analyser. Total Protein was estimated by Biuret method using Chemistry Analyser and Vitamin C by HPLC using 18C column with standards. Ethical Clearance approval was taken from the institutional ethics committee of Grant Government Medical College and Sir J. J. Group of Hospitals, Mumbai and informed consents along with details of patients were taken prior to the study. Statistical evaluation was done by ANOVA test using Minitab 17 software. The other variables were statistically analysed with Pearson correlation. Statistical significance was accepted at $P<0.05$ and data were interpreted using 95% confidence interval.

RESULTS

In our study, dopamine levels were raised in the newly diagnosed TB Category I (CAT I) while GABA, total proteins and vitamin C levels were low when compare to patients with multidrug-resistance (MDR). Significant low levels of dopamine and GABA were observed in TB patients as compared to healthy controls, with age, sex wise distribution in different socioeconomic status as shown in table 1 and 4. There is positive correlation among

Dopamine values, while negative correlation in GABA values as shown in table 2. Also, significant negative correlation among Dopamine/GABA, Dopamine/Total protein and GABA/Total Protein levels in seen [table 3] as the levels of dopamine, GABA, Total protein are lowered in MDR TB due to progression of disease.

TABLE 1: Age, Dopamine, GABA and Total Protein Levels in Control and Pulmonary Tuberculosis.

Group (n=50)	Age (Years)	Dopamine (pg/ml)	GABA(ng/ml)	Protein(g/dl)	Vitamin C(µg/L)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Control	36.86 ±13.32	744.14 ±170.28	86.88 ±8.69	6.75± 0.377	11.48± 1.73
Pulmonary Tuberculosis					
CAT I	33.9 ±13.27	1036.64 ± 212.71	57.38 ± 4.68	4.768 ±0.39	8.3±0.46
MDR	36.26 ± 14.39	139.36 ± 90.27	19.16 ± 5.63	4.404 ± 0.41	5.7±0.42

Table 2: Correlations among Dopamine and GABA in Control and Pulmonary Tuberculosis.

Group	Dopamine/Dopamine		GABA/GABA	
	r-value	P-value	r-value	P-value
Control / CAT I	0.66	0.249	-0.012	0.932
Control / MDR	0.021	0.887	-0.055	0.706
CAT I / MDR	0.164	0.255	-0.098	0.496

Table 3: Correlations among Dopamine, GABA and Protein in Control and TB.

Group	Dopamine /GABA		Dopamine /Protein		GABA/ Protein	
	r-value	P-value	r -value	P- value	r -value	P-value
Control /Control	0.092	0.524	0.114	0.429	-0.287	0.044
Pulmonary Tuberculosis						
Control/CAT I	-0.102	0.481	-0.098	0.500	0.052	0.718
Control/ MDR	-0.516	0.000	0.096	0.507	-0.031	0.829
CAT I/ CAT I	-0.176	0.220	0.104	0.474	-0.138	0.338
CAT I/ MDR	-0.268	0.060	0.217	0.130	-0.310	0.029
MDR / MDR	0.102	0.480	-0.013	0.930	-0.024	0.868

Table 4: Socioeconomic Status Distributions in Pulmonary Tuberculosis.

Socioeconomic class	I	II	III	IV	V
No. of cases (CAT I)	0	1	21	14	14
No. of cases (MDR)	0	10	10	14	16

DISCUSSION

GABA plays the principal role in reducing neuronal excitability throughout the nervous system. In this study we found the significant decrease in neurotransmitters, Dopamine,

GABA, and Total protein than the normal levels in tuberculosis patients in age sex matched in different socioeconomic status groups.[8]

In our study, the dopamine levels in the newly diagnosed TB patients categorised as Category I were initially seen to be raised due to the accumulation of dopamine in the blood system. The reason behind this increase was the decreased catabolism of the existing dopamine, in the TB patients due to deficiency of Vitamin C it is a cofactor in the synthesis of norepinephrine from dopamine.[9, 10, 11, 12] Decreased levels of plasma vitamin C could be associated with low levels of norepinephrine but increased levels of dopamine. Since the existing catecholamines are excreted through urine in TB patients, the levels of dopamine are found to be decreased gradually as the disease progresses. Pyridoxal phosphate is a cofactor in the biosynthesis of five important neurotransmitters: serotonin, dopamine, epinephrine, norepinephrine and GABA.[13] One more important factors involved in TB is malnutrition and are deficient in many essential nutrients.

The increased catecholamine levels have a beneficial physiological effect in either “fight” or “flight” responses. Catecholamines, like norepinephrine and normetanephrine, are found to be released by both innate and adaptive immune cells, in contrast with classifying them only as neurotransmitters and hormones. Their role in immunity and inflammation has been evidently reported in many studies.[14] Interestingly Alaniz et al. have shown that dopamine β-hydroxylase does not produce epinephrine and norpeineprhine are more susceptible to TB and these finding also support our study.[15]

CONCLUSION

It is important to understand nutritional status along with anti-TB drugs in the treatment of TB patients. Also, supplementation of various vitamins like Vitamin C, Vitamin B_6 and proteins is necessary, which plays essential role in the metabolism of Dopamine and GABA and other vital neurotransmitters like norepinephrine and helps maintain their levels. Consideration of these factors will eventually decrease many adverse effects of the TB treatment like depression, disturbed metabolism, psychic strokes etc.

ACKNOWLEDGEMENTS: We thank R.M. Posture for being very supportive to carry out this work.

Funding source: This work was supported by Revised National Tuberculosis Control Program (RNTCP) [Grant number: Jt. DHS/RNTCP/Proporsal/40068-79/14]

Conflicts of interest: The authors declare no conflict of interest.

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